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NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	AUG 10	Time limit for inactive STN sessions doubles to 40 minutes
NEWS 3	AUG 18	COMPENDEX indexing changed for the Corporate Source (CS) field
NEWS 4	AUG 24	ENCOMPLIT/ENCOMPLIT2 reloaded and enhanced
NEWS 5	AUG 24	CA/CAplus enhanced with legal status information for U.S. patents
NEWS 6	SEP 09	50 Millionth Unique Chemical Substance Recorded in CAS REGISTRY
NEWS 7	SEP 11	WPIDS, WPINDEX, and WPIX now include Japanese FTERM thesaurus
NEWS 8	OCT 21	Derwent World Patents Index Coverage of Indian and Taiwanese Content Expanded
NEWS 9	OCT 21	Derwent World Patents Index enhanced with human translated claims for Chinese Applications and Utility Models
NEWS 10	NOV 23	Addition of SCAN format to selected STN databases
NEWS 11	NOV 23	Annual Reload of IFI Databases
NEWS 12	DEC 01	FRFULL Content and Search Enhancements
NEWS 13	DEC 01	DGENE, USGENE, and PCTGEN: new percent identity feature for sorting BLAST answer sets
NEWS 14	DEC 02	Derwent World Patent Index: Japanese FI-TERM thesaurus added
NEWS 15	DEC 02	PCTGEN enhanced with patent family and legal status display data from INPADOCDB
NEWS 16	DEC 02	USGENE: Enhanced coverage of bibliographic and sequence information
NEWS 17	DEC 21	New Indicator Identifies Multiple Basic Patent Records Containing Equivalent Chemical Indexing in CA/CAplus
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NEWS EXPRESS MAY 26 09 CURRENT WINDOWS VERSION IS V8.4,
AND CURRENT DISCOVER FILE IS DATED 06 APRIL 2009.

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FILE 'HOME' ENTERED AT 17:26:33 ON 19 JAN 2010

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.22	0.22

FILE 'REGISTRY' ENTERED AT 17:26:48 ON 19 JAN 2010
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 18 JAN 2010 HIGHEST RN 1202470-25-4
DICTIONARY FILE UPDATES: 18 JAN 2010 HIGHEST RN 1202470-25-4

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TSCA INFORMATION NOW CURRENT THROUGH June 26, 2009.

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> s flupirtine
L1 3 FLUPIRTINE

=> d l1 1-3

L1 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2010 ACS on STN
RN 156094-11-0 REGISTRY
ED Entered STN: 01 Jul 1994
CN Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl-
(5α,6α)-, mixt. with ethyl
[2-amino-6-[[(4-fluorophenyl)methyl]amino]-3-pyridinyl]carbamate (9CI)
(CA INDEX NAME)

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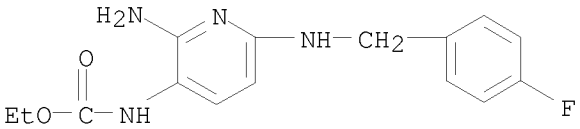
OTHER CA INDEX NAMES:
CN Carbamic acid, [2-amino-6-[[(4-fluorophenyl)methyl]amino]-3-pyridinyl]-, ethyl ester, mixt. contg. (9CI)
OTHER NAMES:
CN Flupirtine-morphine mixt.
CN Morphine-flupirtine mixt.
FS STEREOSEARCH
MF C17 H19 N O3 . C15 H17 F N4 O2
CI MXS
SR CA
LC STN Files: CA, CAPLUS, IMSPATENTS, IMSRESEARCH, USPATFULL

CM 1

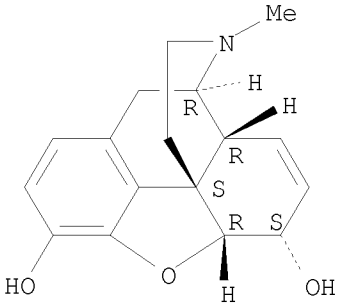
CRN 56995-20-1
CMF C15 H17 F N4 O2



CM 2

CRN 57-27-2
CMF C17 H19 N O3

Absolute stereochemistry. Rotation (-).



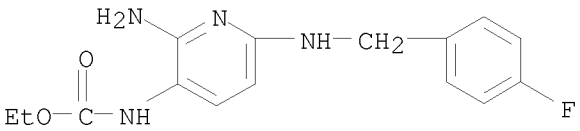
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2010 ACS on STN
RN 75507-68-5 REGISTRY
ED Entered STN: 16 Nov 1984
CN Carbamic acid, N-[2-amino-6-[[(4-fluorophenyl)methyl]amino]-3-pyridinyl]-, ethyl ester, (2Z)-2-butenedioate (1:1) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Carbamic acid, [2-amino-6-[[(4-fluorophenyl)methyl]amino]-3-pyridinyl]-,

ethyl ester, (2Z)-2-butenedioate (1:1) (9CI)
CN Carbamic acid, [2-amino-6-[[(4-fluorophenyl)methyl]amino]-3-pyridinyl]-, ethyl ester, (Z)-2-butenedioate (1:1)
OTHER NAMES:
CN Flupirtine maleate
CN W 2964M
FS STEREOSEARCH
DR 56995-21-2
MF C15 H17 F N4 O2 . C4 H4 O4
LC STN Files: ADISINSIGHT, BIOSIS, CA, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, EMBASE, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

CM 1

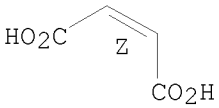
CRN 56995-20-1
CMF C15 H17 F N4 O2



CM 2

CRN 110-16-7
CMF C4 H4 O4

Double bond geometry as shown.



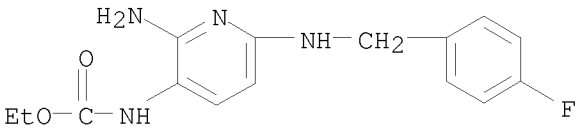
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

56 REFERENCES IN FILE CA (1907 TO DATE)
56 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2010 ACS on STN
RN 56995-20-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN Carbamic acid, N-[2-amino-6-[[(4-fluorophenyl)methyl]amino]-3-pyridinyl]-, ethyl ester (CA INDEX NAME)
OTHER CA INDEX NAMES:

10574438

CN Carbamic acid, [2-amino-6-[[(4-fluorophenyl)methyl]amino]-3-pyridinyl]-, ethyl ester (9CI)
OTHER NAMES:
CN D 9998
CN Flupirtine
CN Katadolon
CN Trancopal Dolo
MF C15 H17 F N4 O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSPRODUCT, IMSRESEARCH, IPA, MEDLINE, MRCK*, PROMT, PROUSDDR, PS, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

191 REFERENCES IN FILE CA (1907 TO DATE)
12 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
192 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file CA, CAPLUS, imspatents, IMSRESEARCH, uspatful

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	13.27	13.49

FILE 'CA' ENTERED AT 17:28:25 ON 19 JAN 2010
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FILE 'CAPLUS' ENTERED AT 17:28:25 ON 19 JAN 2010
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FILE 'IMSPATENTS' ENTERED AT 17:28:25 ON 19 JAN 2010

FILE 'IMSRESEARCH' ENTERED AT 17:28:25 ON 19 JAN 2010

FILE 'USPATFULL' ENTERED AT 17:28:25 ON 19 JAN 2010

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CA INDEXING COPYRIGHT (C) 2010 AMERICAN CHEMICAL SOCIETY (ACS)

```
=> s l1
L2         606 L1

=> s flupirtine and morphine
L3         514 FLUPIRTINE AND MORPHINE

=> s l2 and l3
L4         216 L2 AND L3

=> s neuropathic
L5       25214 NEUROPATHIC

=> s neuro? pain
L6       23473 NEURO? PAIN

=> s l6 and l4
L7          23 L6 AND L4

=> dup rem
ENTER L# LIST OR (END):l7
DUPLICATE IS NOT AVAILABLE IN 'IMSPATENTS, IMSRESEARCH'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L7
L8           14 DUP REM L7 (9 DUPLICATES REMOVED)

=> s l8 and py<2004
L9            0 L8 AND PY<2004

=> d l8 1-14 ibib, kwic

L8   ANSWER 1 OF 14  CA  COPYRIGHT 2010 ACS on STN     DUPLICATE 1
ACCESSION NUMBER:        151:502914  CA
TITLE:                   Methods and compositions for the management of pain
                         using ω-conotoxins
INVENTOR(S):             Cooke, Ian; Goodchild, Colin Stanley
PATENT ASSIGNEE(S):      CNSBio Pty. Ltd., Australia
SOURCE:                  PCT Int. Appl., 79pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     ---------------     ----   --------    --------------------    --------
     WO 2009135258        A1    20091112    WO 2009-AU563           20090506
         W:  AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
             CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES,
             FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE,
             KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
             ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH,
             PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ,
             TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU,
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IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI,
SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.: US 2008-50869P P 20080506
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Pain
(neuropathic pain; ω-conotoxins for management of pain)
IT 56995-20-1, Flupirtine 150812-12-7, Retigabine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination; ω-conotoxins for management of pain)
IT 57-27-2, Morphine, biological studies 60142-96-3, Gabapentin
RL: PAC (Pharmacological activity); BIOL (Biological study)
(ω-conotoxins for management of pain)

L8 ANSWER 2 OF 14 CA COPYRIGHT 2010 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 150:563641 CA
TITLE: Preparation of indole compounds and methods for treating visceral pain and other conditions mediated by NOS or 5HT1D/1B receptors
INVENTOR(S): Maddaford, Shawn; Ramnauth, Jailall; Rakhit, Suman; Patman, Joanne; Renton, Paul; Annedi, Subhash C.; Andrews, John S.; Mladenova, Gabriela
PATENT ASSIGNEE(S): NeurAxon, Inc., Can.
SOURCE: PCT Int. Appl., 140pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009062319	A1	20090522	WO 2008-CA2047	20081117
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20090192157	A1	20090730	US 2008-272775	20081117

PRIORITY APPLN. INFO.: US 2007-988757P P 20071116
US 2008-133930P P 20080703
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 150:563641
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Pain
(neuropathic pain; preparation of indole compds. and methods for treating visceral pain and other conditions mediated by NOS or 5HT1D/1B receptors)

IT 50-24-8, Prednisolone 50-33-9, Phenylbutazone, biological studies 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-78-2, Aspirin 51-12-7, Nialamide 51-71-8, Phenelzine 52-52-8, 1-Aminocyclopentanecarboxylic acid 53-06-5, Cortisone 53-86-1, Indomethacin 54-92-2, Iproniazid 56-40-6, Glycine, biological studies 57-41-0, Phenytoin 57-42-1, Meperidine 59-63-2, Isocarboxazid 61-68-7, Mefenamic acid 62-44-2, Phenidin 65-45-2, Salicylamide 68-89-3, Metamizol 72-69-5 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 77-07-6, Levorphanol 83-98-7, OrPhenadrine 99-66-1 108-01-0, Deanol 113-53-1, Dothiepin 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 125-58-6, Levomethadone 125-71-3, Dextromethorphan 129-20-4, Oxyphenbutazone 155-09-9, Tranylcypromine 298-46-4, Carbamazepine 302-41-0, Piritramide 303-48-0, Norclomipramine 303-49-1, Clomipramine 315-72-0, Opipramol 357-56-2, Dextromoramide 359-83-1, Pentazocine 437-38-7, Fentanyl 438-60-8, Protriptyline 465-65-6, Naloxone 466-99-9, Hydromorphone 469-62-5, Dextropropoxyphene 469-79-4, Ketobemidone 530-78-9, Flufenamic acid 555-57-7, Pargyline 644-62-2, Meclofenamic acid 655-05-0, Thozalinone 726-99-8, Fluorofelbamate 739-71-9, Trimipramine 768-94-5, Amantadine 853-34-9, Kebuzone 915-30-0, Diphenoxylate 938-73-8, Ethenzamide 1668-19-5, Doxepin 1977-11-3, Perlapine 2210-63-1, Mofebutazone 3286-46-2, Sulbutiamine 3362-45-6, Noxiptilin 4317-14-0, Amitriptylin oxide 4394-00-7, Niflumic acid 4498-32-2, Dibenzepin 4757-55-5, Dimetacrine 5104-49-4, Flurbiprofen 5118-29-6, Melitracen 5560-72-5, Iprindole 6740-88-1, Ketamine 6829-98-7, Imipramine N-oxide 7439-93-2, Lithium, biological studies 10262-69-8, Maprotiline 10321-12-7, Propizepine 13669-70-0, Nefopam 14028-44-5, Amoxapine 14521-96-1, Etorphine 15301-93-6, Tofenacin 15307-86-5, Diclofenac 15574-96-6, Pizotyline 15676-16-1, Sulpiride 15687-27-1, Ibuprofen 17780-72-2, Clorgyline 18464-39-6, Caroxazone 19794-93-5, Trazodone 19982-08-2, Memantine 20290-10-2, Morphine -6-glucuronide 20594-83-6, Nalbuphine 21730-16-5, Metapramine 22071-15-4, Ketoprofen 22204-53-1, Naproxen 22345-47-7, Tofisopam 22494-42-4, Diflunisal 23047-25-8, Lofepramine 23651-95-8, Droxidopa 24219-97-4, Mianserin 24305-27-9, Thyroliberin 24526-64-5, Nomifensine 24701-51-7, Demexiptiline 25451-15-4, Felbamate 25905-77-5, Minaprine 26171-23-3, Tolmetin 26629-87-8, Oxaflozane 27203-92-5, Tramadol 28721-07-5, Oxcarbazepine 29218-27-7, Toloxatone 29679-58-1, Fenoprofen 29975-16-4, Estazolam 30223-48-4, Fluacizine 30544-47-9, Etofenamate 31721-17-2, Quinupramine 32359-34-5, Medifoxamine 33005-95-7, Tiaprofenic acid 34552-84-6, Isoxicam 34911-55-2, Bupropion 35764-73-9, Fluotracen 35941-65-2, Butriptyline 36322-90-4, Piroxicam 37115-32-5, Adinazolam 38194-50-2, Sulindac 40828-46-4, Suprofen 41717-30-0, Befuraline 42408-82-2, Butorphanol 42924-53-8, Nabumetone 46817-91-8, Viloxazine 51022-73-2, Zometapine 51248-68-1 51931-66-9, Tilidine 52463-83-9, Pinazepam 52485-79-7, Buprenorphine 52942-31-1, Etoperidone 53164-05-9, Acemetacin 53179-11-6, Loperamide 53648-55-8, Dezocine 53808-88-1, Lonazolac 54188-38-4, Metralindole 54340-58-8, Meptazinol 54403-19-9, Sercloremine 54739-18-3, Fluvoxamine 54739-19-4, Clovoxamine 54910-89-3, Fluoxetine 56030-54-7 56775-88-3, Zimelidine 56995-20-1, Flupirtine 57262-94-9, Setiptiline

57574-09-1, Amineptine 57982-78-2, Budipine 59729-33-8, Citalopram 59804-37-4, Tenoxicam 59859-58-4, Femoxetine 60142-96-3, Gabapentin 60662-16-0, Binodaline 60719-82-6, Alaproclate 60762-57-4, Pirlindole 60929-23-9, Indeloxazine 61413-54-5, Rolipram 61869-08-7, Paroxetine 62305-86-6, Orotirelin 62473-79-4, Teniloxazine 63638-91-5, Brofaromine 63758-79-2, Indalpine 65165-99-3 66532-85-2, Propacetamol 66644-81-3, Veralipride 66834-24-0, Cianopramine 67469-69-6, Vanoxerine 67765-04-2, Enefexine 68134-81-6, Gacyclidine 70374-39-9, Lornoxicam 71125-38-7, Meloxicam 71195-58-9, Alfentanyl 71320-77-9, Moclobemide 71620-89-8, Reboxetine 71827-56-0, Clemeprol 72714-74-0, Viqualine 72797-41-2, Tianeptine 73815-11-9, Cimoxatone 74103-06-3, Ketorolac 75991-50-3, Dazepinil 76496-68-9, Levoprotiline 77518-07-1, Amiflamine 78113-47-0 79467-22-4, Bipenamol 79617-96-2, Sertraline 79944-58-4, Idazoxan 80018-06-0, Fengabine 80410-36-2, Fezolamine 83015-26-3, Atomoxetine 83366-66-9, Nefazodone 83891-03-6, Norfluoxetine 84057-84-1, Lamotrigine 85650-52-8, Mirtazapine 86811-09-8, Litoxetine 87051-43-2, Ritanserin 89875-86-5, Tiflucarbine 90243-66-6, Montirelin 90293-01-9, Bifemelane 92623-85-3, Milnacipran 93413-69-5, Venlafaxine 93438-65-4, Conantokin G 94011-82-2, Bazinaprine 96206-92-7, 2-Methyl-6-(phenylethynyl)pyridine 97205-34-0, Nebracetam 97240-79-4, Topiramate 103628-46-2, Sumatriptan 104054-27-5, Atipamezole 104454-71-9, Ipenoxazone 106650-56-0, Sibutramine 112922-55-1, Ericlamine 112924-45-5, Dexanabinol 116539-59-4, Duloxetine 117414-74-1, Midafotel 117571-54-7 120667-19-8 121679-13-8, Naratriptan 123653-11-2, N-[2-(Cyclohexyloxy)-4-nitrophenyl]methanesulfonamide 128196-01-0, Escitalopram 128298-28-2, Remacemide 132472-31-2, (3E)-2-Amino-4-(phosphonomethyl)-3-heptenoic acid 132875-61-7, Remifentanyl 134564-82-2, Befloxatone 135025-56-8, 7-Chlorothiokynurenic acid 137159-92-3, Aptiganel 137433-06-8, (3S,4AR,6S,8aR)-decahydro-6-(phosphonomethyl)-3-isoquinolinecarboxylic acid 138047-56-0, (3R,4S)-rel-3,4-Dihydro-3-[4-hydroxy-4-(phenylmethyl)-1-piperidinyl]-2H-1-benzopyran-4,7-diol 139051-78-8, (2R,4S)-rel-5,7-Dichloro-1,2,3,4-tetrahydro-4-[[(phenylamino)carbonyl]amino]-2-quinolinecarboxylic acid 139264-17-8, Zolmitriptan 143322-58-1, Eletriptan 143850-75-3 144034-80-0, Rizatriptan 144912-63-0 149756-73-0, FPL-12495 150812-12-7, Retigabine 153322-05-5, Lanicemine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(codrug; preparation of indole compds. and methods for treating visceral pain and other conditions mediated by NOS or 5HT1D/1B receptors)

IT 57-27-2, Morphine, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tolerance to and as codrug; preparation of indole compds. and methods for treating visceral pain and other conditions mediated by NOS or 5HT1D/1B receptors)

L8 ANSWER 3 OF 14 CA COPYRIGHT 2010 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 150:539562 CA
TITLE: Preparation of 3,5-Substituted indole compounds having NOS and norepinephrine reuptake inhibitory activity
INVENTOR(S): Annedi, Subhash C.; Maddaford, Shawn; Ramnauth, Jailall; Renton, Paul; Rakhit, Suman; Andrews, John S.; Mladenova, Gabriela

10574438

PATENT ASSIGNEE(S): NeurAxon, Inc., Can.
SOURCE: PCT Int. Appl., 101pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009062318	A1	20090522	WO 2008-CA2033	20081117
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20090131503	A1	20090521	US 2008-272656	20081117

PRIORITY APPLN. INFO.:
US 2007-988741P P 20071116
US 2008-133975P P 20080703

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 150:539562; MARPAT 150:539562
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Pain
(neuropathic pain, chemotherapy induced neuropathic pain; preparation of 3,5-substituted indole compds. having NOS and norepinephrine reuptake inhibitory activity for treating pain, psychiatric disorders, and other diseases)

IT Pain
(neuropathic pain; preparation of 3,5-substituted indole compds. having NOS and norepinephrine reuptake inhibitory activity for treating pain, psychiatric disorders, and other diseases)

IT 50-24-8, Prednisolone 50-33-9, Phenylbutazone, biological studies 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-78-2, Aspirin 51-12-7, Nialamide 51-71-8, Phenelzine 52-52-8, 1-Aminocyclopentanecarboxylic acid 53-06-5, Cortisone 53-86-1, Indomethacin 54-92-2, Iproniazid 56-40-6, Glycine, biological studies 57-41-0, Phenytoin 57-42-1, Meperidine 59-63-2, Isocarboxazid 61-68-7, Mefenamic acid 62-44-2, Phenidin 65-45-2, Salicylamide 68-89-3, Metamizol 72-69-5 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 77-07-6, Levorphanol 83-98-7, OrPhenadrine 99-66-1 108-01-0, Deanol 113-53-1, Dothiepin 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 125-58-6, Levomethadone 125-71-3, Dextromethorphan 129-20-4, Oxyphenbutazone 155-09-9, Tranylcypromine 298-46-4, Carbamazepine 302-41-0, Piritramide 303-48-0, Norclomipramine 303-49-1, Clomipramine 315-72-0, Opipramol 357-56-2, Dextromoramide 359-83-1, Pentazocine 437-38-7, Fentanyl

438-60-8, Protriptyline 465-65-6, Naloxone 466-99-9, Hydromorphone 469-62-5, Dextropropoxyphene 469-79-4, Ketobemidone 479-92-5, Propyphenazone 530-78-9, Flufenamic acid 555-57-7, Pargyline 644-62-2, Meclofenamic acid 655-05-0, Thozalinone 726-99-8, Fluorofelbamate 739-71-9, Trimipramine 768-94-5, Amantadine 853-34-9, Kebuzone 915-30-0, Diphenoxylate 938-73-8, Ethenzamide 1668-19-5, Doxepin 1977-11-3, Perlapine 2210-63-1, Mofebutazone 3286-46-2, Sulbutiamine 3362-45-6, Noxiptilin 4317-14-0, Amitriptyline oxide 4394-00-7, Niflumic acid 4498-32-2, Dibenzepin 4757-55-5, Dimetacrine 5104-49-4, Flurbiprofen 5118-29-6, Melitracen 5560-72-5, Iprindole 6740-88-1, Ketamine 6829-98-7, Imipramine N-oxide 7439-93-2, Lithium, biological studies 10262-69-8, Maprotiline 10321-12-7, Propizepine 13669-70-0, Nefopam 14028-44-5, Amoxapine 14521-96-1, Etorphine 15301-93-6, Tofenacin 15307-86-5, Diclofenac 15574-96-6, Pizotyline 15676-16-1, Sulpiride 15687-27-1, Ibuprofen 17780-72-2, Clorgyline 18464-39-6, Caroxazone 19794-93-5, Trazodone 19982-08-2, Memantine 20290-10-2, Morphine-6-glucuronide 20594-83-6, Nalbuphine 21730-16-5, Metapramine 22071-15-4, Ketoprofen 22204-53-1, Naproxen 22345-47-7, Tofisopam 22494-42-4, Diflunisal 23047-25-8, Lofepramine 23651-95-8, Droxidopa 24219-97-4, Mianserin 24305-27-9, Thyroliberin 24526-64-5, Nomifensine 24701-51-7, Demexiptiline 25451-15-4, Felbamate 25905-77-5, Minaprine 26171-23-3, Tolmetin 26629-87-8, Oxaflozane 27203-92-5, Tramadol 28721-07-5, Oxcarbazepine 29218-27-7, Toloxatone 29679-58-1, Fenoprofen 29975-16-4, Estazolam 30223-48-4 30544-47-9, Etofenamate 31721-17-2, Quinupramine 32359-34-5, Medifoxamine 33005-95-7, Tiaprofenic acid 34552-84-6, Isoxicam 34911-55-2, Bupropion 35764-73-9, Fluotracen 35941-65-2, Butriptyline 36322-90-4, Piroxicam 37115-32-5, Adinazolam 38194-50-2, Sulindac 40828-46-4, Suprofen 41717-30-0, Befuraline 42408-82-2, Butorphanol 42924-53-8, Nabumetone 46817-91-8, Viloxazine 51022-73-2, Zometapine 51248-68-1 51931-66-9, Tilidine 52463-83-9, Pinazepam 52485-79-7, Buprenorphine 52942-31-1, Etoperidone 53164-05-9, Acemetacin 53179-11-6, Loperamide 53648-55-8, Dezocine 53808-88-1, Lonazolac 54188-38-4 54403-19-9 54739-18-3, Fluvoxamine 54739-19-4, Clovoxamine 54910-89-3, Fluoxetine 56030-54-7 56775-88-3, Zimelidine 56995-20-1, Flupirtine 57262-94-9, Setiptiline 57574-09-1, Amineptine 57982-78-2, Budipine 59729-33-8, Citalopram 59804-37-4, Tenoxicam 59859-58-4, Femoxetine 60142-96-3, Gabapentin 60662-16-0 60719-82-6, Alaproclate 60762-57-4, Pirlindole 60929-23-9, Indeloxazine 61413-54-5, Rolipram 61869-08-7, Paroxetine 62305-86-6 62473-79-4, Teniloxazine 63638-91-5, Brofaromine 63758-79-2, Indalpine 66532-85-2, Propacetamol 66644-81-3, Veralipride 66834-24-0, Cianopramine 67469-69-6, Vanoxerine 67765-04-2 68134-81-6, Gacyclidine 70374-39-9, Lornoxicam 71125-38-7, Meloxicam 71195-58-9, Alfentanyl 71320-77-9, Moclobemide 71620-89-8, Reboxetine 71827-56-0, Clemeprol 72714-74-0, Viqualine 72797-41-2, Tianeptine 73815-11-9, Cimoxatone 74103-06-3, Ketorolac 75991-50-3, Dazepinil 76496-68-9, Levoprotiline 77518-07-1, Amiflamine 79467-22-4, Bipenamol 79617-96-2, Sertraline 79944-58-4, Idazoxan 80018-06-0, Fengabine 80410-36-2 83015-26-3, Atomoxetine 83366-66-9, Nefazodone 83891-03-6, Norfluoxetine 84057-84-1, Lamotrigine 85650-52-8, Mirtazapine 86811-09-8, Litoxetine 87051-43-2, Ritanserin 89875-86-5, Tiflucarbine 90243-66-6, Montirelin 90293-01-9, Bifemelane 92623-85-3, Milnacipran 93413-69-5, Venlafaxine 93438-65-4, Conantokin G 94011-82-2, Bazinaprine 96206-92-7,

2-Methyl-6-(phenylethynyl)pyridine 97205-34-0, Nebracetam 97240-79-4, Topiramate 103628-46-2, Sumatriptan 104054-27-5, Atipamezole 104454-71-9, Ipenoxazone 106650-56-0, Sibutramine 112922-55-1, Cericlamine 112924-45-5, Dexanabinol 116539-59-4, Duloxetine 117414-74-1, Midafotel 117571-54-7 120667-19-8 121679-13-8, Naratriptan 123653-11-2, N-[2-(Cyclohexyloxy)-4-nitrophenyl]methanesulfonamide 128196-01-0, Escitalopram 128298-28-2, Remacemide 132472-31-2, (3E)-2-Amino-4-(phosphonomethyl)-3-heptenoic acid 132875-61-7, Remifentanyl 134564-82-2, Befloxatone 135025-56-8, 7-Chlorothiokynurenic acid 137159-92-3, Aptiganel 137433-06-8, (3S,4AR,6S,8aR)-decahydro-6-(phosphonomethyl)-3-isoquinolinecarboxylic acid 138047-56-0, (3R,4S)-rel-3,4-Dihydro-3-[4-hydroxy-4-(phenylmethyl)-1-piperidinyl]-2H-1-benzopyran-4,7-diol 139051-78-8, (2R,4S)-rel-5,7-Dichloro-1,2,3,4-tetrahydro-4-[[(phenylamino)carbonyl]amino]-2-quinolinecarboxylic acid 139264-17-8, Zolmitriptan 142235-88-9, 3-(Phosphonomethyl)-L-phenylalanine 143322-58-1, Eletriptan 143850-75-3 144034-80-0, Rizatriptan 144912-63-0 149756-73-0 150812-12-7, Retigabine 153322-05-5, Lanicemine 153504-81-5, Licostinel
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(codrug; preparation of 3,5-substituted indole compds. having NOS and norepinephrine reuptake inhibitory activity for treating pain, psychiatric disorders, and other diseases)

IT 57-27-2, Morphine, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tolerance to and as codrug; preparation of 3,5-substituted indole compds. having NOS and norepinephrine reuptake inhibitory activity for treating pain, psychiatric disorders, and other diseases)

L8 ANSWER 4 OF 14 CA COPYRIGHT 2010 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 151:558698 CA
TITLE: Co-crystals of duloxetine and co-crystal formers for the treatment of pain
INVENTOR(S): Buschmann, Heimut Heinrich; Sola Carandell, Luis; Benet Buchholz, Jordi; Ceron Bertran, Jordi Carles
PATENT ASSIGNEE(S): Laboratorios del Dr. Esteve S. A., Spain
SOURCE: Eur. Pat. Appl., 23pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 2123626	A1	20091125	EP 2008-384009	20080521
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, MK, RS				
WO 2009141144	A1	20091126	WO 2009-EP3617	20090520
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,				

ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH,
PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ,
TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU,
IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI,
SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: EP 2008-384009 A 20080521

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Nerve, disease
(diabetic neuropathy, pain, treatment of;
co-crystals of duloxetine and co-crystal formers for treatment of pain)

IT Pain
(neuropathic pain, treatment of; co-crystals of
duloxetine and co-crystal formers for treatment of pain)

IT 50-33-9, Phenylbutazone, biological studies 50-35-1, Thalidomide
50-47-5, Desipramine 50-48-6 50-49-7, Imipramine 50-78-2,
Acetylsalicylic acid 53-86-1, In-domethacin 57-27-2, Morphine
, biological studies 57-41-0, Phenytoin 57-42-1, Pethidine 61-68-7,
Mefenamic acid 62-44-2, Phenidin 62-67-9, Nalorphine 64-86-8,
Colchicine 65-45-2, Salicylamide 68-41-7, Cycloserine 68-89-3,
Metamizol 72-69-5 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3,
Codeine 76-58-4, Ethylmorphine 77-07-6, Levorphanol 99-66-1,
Valproic acid 103-90-2, Paracetamol 125-28-0, Dihydrocodeine
125-29-1, Hydrocodone 125-58-6, Levomethadone 125-71-3,
Dextromethorphan 129-20-4, Oxyphenbutazone 131-48-6, Aceneuramic acid
137-58-6, Lidocaine 152-02-3, Levallorphan 298-46-4, Carbamazepine
302-41-0, Piritramide 322-79-2, Triflusal 328-90-5,
(2-Hydroxy-4-trifluoromethyl benzoic acid) 357-56-2, Dextromoramide
359-83-1, Pentazocine 361-37-5, Methysergide 404-86-4, Capsaicine
437-38-7, Fentanyl 465-65-6, Naloxone 466-99-9, Hydromorphone
469-62-5, Dextropropoxyphene 469-79-4, Ketobemidone 511-12-6,
Dihydroergotamine 530-78-9, Flufenamic acid 561-27-3, Diacetylmorphine
644-62-2, Meclofenamic acid 853-34-9, Kebuzone 915-30-0, Diphenoxylate
938-73-8, Ethenzamide 1134-47-0, Baclofen 1477-40-3, Levomethadyl
acetate 1972-08-3, Dronabinol 1977-10-2, Loxapine 2210-63-1,
Mofebutazone 2438-72-4, Bufexamac 4205-90-7, Clonidine 4368-28-9,
Tetrodotoxin 4394-00-7, Niflumic acid 5003-48-5, Benorylate
5104-49-4, Flurbiprofen 5728-52-9, Felbinac 6064-83-1, Fosfosal
6740-88-1, Ketamine 12794-10-4, Benzodiazepine 13539-59-8, Apazone
13669-70-0, Ne-fopam 13710-19-5, Tolfenamic acid 13956-29-1,
Cannabidiol 14521-96-1, Etorphine 15307-86-5, Diclofenac 15574-96-6,
Pizotifen 15687-27-1, Ibuprofen 16590-41-3, Naltrexone 17692-51-2,
Metergoline 18046-21-4, Fentiazac 18471-20-0, Ditazole 19982-08-2,
Memantine 20290-10-2, Morphine-6-glucuronide 20594-83-6,
Nalbuphine 21256-18-8, Oxaprozin 22071-15-4, Ketoprofen 22131-79-9,
4-Allyloxy-3 chlorophenylacetic acid 22204-53-1, Naproxen 22494-42-4,
Diflunisal 22760-18-5, Proquazone 25775-90-0, Zucapsaicin
26171-23-3, Tolmetin 27035-30-9, Oxametacin 27203-92-5, Tramadol
28721-07-5, Oxcarbazepine 29679-58-1, Fenoprofen 30544-47-9,
Etofenamate 31793-07-4, Pirprofen 31828-71-4, Mexiletine 33005-95-7,
Tiaprofenic acid 34148-01-1, Clidanac 34552-84-6, Isoxicam
36322-90-4, Piroxicam 36330-85-5, Fenbufen 38194-50-2, Sulindac
38396-39-3, Bupivacaine 41340-25-4, Etodolac 42408-82-2, Butorphanol

42924-53-8, Nabumetone 51022-71-0, Nabilone 51146-56-6, S-(+)-Ibuprofen 51543-39-6, Esflurbiprofen 51579-82-9, Amfenac 51803-78-2, Nimesulide 51931-66-9, Tilidine 52443-21-7, Glucametacin 52468-60-7, Flunarizine 52485-79-7, Buprenorphine 53164-05-9, Acemetacin 53179-11-6, Loperamide 53648-55-8, Dezocine 53808-88-1, Lonazolac 54340-58-8, Meptazinol 54910-89-3, Fluoxetine 55096-26-9, Nalmefene 56030-54-7, Sufentanil 56105-81-8 56187-89-4, Ximoprofen 56355-17-0, Zoliprofen 56995-20-1, Flupirtine 57132-53-3, Proglumetacin 59708-52-0, Carfentanil 59804-37-4, Tenoxicam 60142-96-3, Gabapentin 66532-85-2, Propaceta-mol 66635-85-6, Anirolac 68291-97-4, Zonisamide 69956-77-0, Pelubiprofen 70374-39-9, Lornoxicam 71002-09-0, Pirazolac 71109-09-6, Vedaprofen 71125-38-7, Meloxicam 71195-57-8, Bicifadine 71195-58-9, Alfentanil 72522-13-5, Eptazocine 73232-52-7, N-Methylnaltrexone bromide 74103-06-3, Ketorolac 74711-43-6, Zaltoprofen 75377-45-6, N-Desmethyl-tramadol 78281-72-8, Nepafenac 78499-27-1, Bermoprofen 78967-07-4, Mofezolac 84057-84-1, Lamotrigine 84057-95-4, Ropivacaine 87344-06-7, Amtolmetin guacil 89796-99-6, Aceclofenac 91503-79-6, Flurbiprofen axetil 91714-94-2, Bromfenac 92623-85-3, Milnacipran 93413-62-8, Desvenlafaxine 93413-69-5, Venlafaxine 95232-68-1, Tenosal 97240-79-4, Topiramate 98819-76-2 99755-59-6, Rotigotine 103420-77-5, Devazepide 103628-46-2, Sumatriptan 107452-89-1, Ziconotide 109543-76-2, Romazarit 112344-52-2, Flobufen 114030-44-3, Dexpemedolac 114716-16-4, Pemedolac 116539-59-4, Duloxetine 121679-13-8, Naratriptan 130641-38-2, Bindarit 132875-61-7, Remifentanil 133865-88-0, Ralfinamide 137945-48-3, Ajulemic acid 139264-17-8, Zolmitriptan 139481-59-7, Candesartan 143322-58-1, Eletriptan 144034-80-0, Rizatriptan 148553-50-8, Prega-balin 150812-12-7, Retigabine 154323-57-6, Almotriptan 158747-02-5, Frovatriptan 162011-90-7, Ro-fecoxib 169590-42-5, Celecoxib 170912-52-4, Doni-triptan 175481-36-4, Lacosamide 175591-23-8, Tapentadol 181695-72-7, Valdecoxib 191732-72-6, Lenalidomide 198470-84-7, Parecoxib 202409-33-4, Etoricoxib 220991-20-8, Lumiracoxib 265114-23-6, Cimicoxib 478296-72-9, Gabapentin enacarbil 808756-71-0, ABT-102
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(co-crystals of duloxetine and co-crystal formers for treatment of pain)

L8 ANSWER 5 OF 14 USPATFULL on STN
ACCESSION NUMBER: 2009:213881 USPATFULL
TITLE: INDOLE COMPOUNDS AND METHODS FOR TREATING VISCERAL PAIN
INVENTOR(S): Maddaford, Shawn, Mississauga, CANADA
Ramnauth, Jailall, Brampton, CANADA
Rakhit, Suman, Mississauga, CANADA
Patman, Joanne, Mississauga, CANADA
Renton, Paul, Toronto, CANADA
Annedi, Subhash C., Mississauga, CANADA
Andrews, John S., Mississauga, CANADA
Mladenova, Gabriela, Thornhill, CANADA

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20090192157	A1	20090730	
APPLICATION INFO.:	US 2008-272775	A1	20081117	(12)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2008-133930P	20080703 (61)
	US 2007-988757P	20071116 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	CLARK & ELBING LLP, 101 FEDERAL STREET, BOSTON, MA, 02110, US	
NUMBER OF CLAIMS:	28	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	12 Drawing Page(s)	
LINE COUNT:	3583	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . can be prevented or treated include migraine headache (with or without aura), chronic tension type headache (CTTH), migraine with allodynia, neuropathic pain, post-stroke pain, chronic headache, chronic pain, acute spinal cord injury, diabetic neuropathy, trigeminal neuralgia, diabetic nephropathy, an inflammatory disease, stroke,. . . neurological damage, HCA, AIDS associated dementia, neurotoxicity, Parkinson's disease, Alzheimer's disease, ALS, Huntington's disease, multiple sclerosis, methamphetamine-induced neurotoxicity, drug addiction, morphine/opioid induced tolerance, dependence, hyperalgesia, or withdrawal, ethanol tolerance, dependence, or withdrawal, epilepsy, anxiety, depression, attention deficit hyperactivity disorder, and psychosis.. . . neurodegeneration, head trauma, CABG associated neurological damage, migraine headache (with or without aura), migraine with allodynia, chronic tension type headache, neuropathic pain, post-stroke pain, opioid induced hyperalgesia, or chronic pain. In particular, 3,5-substituted indole compounds are useful for treating migraine, with or. . .

SUMM . . . invention

Class	Examples
Opioid	alfentanil, butorphanol, buprenorphine, codeine, dextromoramide, dextropropoxyphene, dezocine, dihydrocodeine, diphenoxylate, etorphine, fentanyl, hydrocodone, hydromorphone, ketobemidone, levorphanol, levomethadone, methadone, meptazinol, morphine, morphine-6-glucuronide, nalbuphine, naloxone, oxycodone, oxymorphone, pentazocine, pethidine, piritramide, remifentanil, sulfentanyl, tilidine, or tramadol
Antidepressant (selective serotonin re-uptake. . .	citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline
	sibutramine, sulbutiamine, sulpiride, teniloxazine, thozalinone, thymoliberin, tianeptine, tiflucarbine, trazodone, tofenacin, tofisopam, toloxatone, tomoxetine, veralipride, viloxazine, viqualine, zimelidine, or zometapine

Antiepileptic carbamazepine, flupirtine, gabapentin, lamotrigine, oxcarbazepine,
phenytoin, retigabine, topiramate, or valproate
Non-steroidal acemetacin, aspirin, celecoxib, deracoxib, diclofenac, diflunisal,
anti- ethenzamide, etofenamate, etoricoxib, fenoprofen, flufenamic acid,
inflammatory. . . budipine; conantokin G;
aspartate delucemine; dexanabinol; dextromethorphan;
antagonist dextropropoxyphen; felbamate; fluorofelbamate; gacyclidine; glycine;
ipenoxazone; kaitocephalin; ketamine; ketobemidone; lanicemine;
licostinel; midafotel; memantine; D-methadone; D-morphine;
milnacipran; neramexane; orphenadrine; remacemide; sulfazocine;
FPL-12,495 (racemide metabolite); topiramate;
(αR)-α-amino-5-
chloro-1-(phosphonomethyl)-1H-benzimidazole-2-propanoic acid; 1-
aminocyclopentane-carboxylic acid;
[5-(aminomethyl)-2-[[[(5S)-9-
chloro-2,3,6,7-tetrahydro-2,3-dioxo-1H-,5H-pyrido[1,2,3-de]quinoxalin-5-yl]acetyl]amino]phenoxy]-acetic acid;
α-amino-2-
. . .

SUMM . . . They include, but are not limited to, paracetamol (i.e., acetaminophen), the nonsteroidal anti-inflammatory drugs (NSAIDs), and opiate drugs such as morphine.

SUMM . . . anticonvulsants inhibit the metabolism of GABA or increase its release. Examples of anticonvulsants include, but are not limited to, carbamazepine, flupirtine, gabapentin, lamotrigine, oxcarbazepine, phenyloin, retigabine, topiramate, and valproate.

SUMM . . . limited to, alfentanil, butorphanol, buprenorphine, codeine, dextromoramide, dextropropoxyphene, dezocine, dihydrocodeine, diphenoxylate, etorphine, fentanyl, hydrocodone, hydromorphone, ketobemidone, levorphanol, levomethadone, methadone, meptazinol, morphine, morphine-6-glucuronide, nalbuphine, naloxone, oxycodone, oxymorphone, pentazocine, pethidine, piritramide, remifentanil, sulfentanyl, tapentadol, tilidine, and tramadol.

DETD The efficacy of the compounds of the invention for the treatment of neuropathic pain was assessed using standard animal models predictive of anti-hyperalgesic and anti-allodynic activity induced by a variety of methods, each described. . .

DETD (a) Chung Model of Injury-induced Neuropathic-like Pain: The experimental designs for the Chung Spinal Nerve Ligation SNL Model assay for neuropathic pain are depicted in the Figure below. Nerve ligation injury was performed according to the method described by Kim and Chung. . .

DETD . . . 5 and 6, respectively). A clear difference between the two enantiomers of compound 6 was observed in this model of neuropathic pain.

IT 50-24-8, Prednisolone 50-33-9, Phenylbutazone, biological studies
50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine
50-78-2, Aspirin 51-12-7, Nialamide 51-71-8, Phenelzine 52-52-8,

1-Aminocyclopentanecarboxylic acid 53-06-5, Cortisone 53-86-1, Indomethacin 54-92-2, Iproniazid 56-40-6, Glycine, biological studies 57-41-0, Phenytoin 57-42-1, Meperidine 59-63-2, Isocarboxazid 61-68-7, Mefenamic acid 62-44-2, Phenidin 65-45-2, Salicylamide 68-89-3, Metamizol 72-69-5 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 77-07-6, Levorphanol 83-98-7, OrPhenadrine 99-66-1 108-01-0, Deanol 113-53-1, Dothiepin 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 125-58-6, Levomethadone 125-71-3, Dextromethorphan 129-20-4, Oxyphenbutazone 155-09-9, Tranylcypromine 298-46-4, Carbamazepine 302-41-0, Piritramide 303-48-0, Norclomipramine 303-49-1, Clomipramine 315-72-0, Opipramol 357-56-2, Dextromoramide 359-83-1, Pentazocine 437-38-7, Fentanyl 438-60-8, Protriptyline 465-65-6, Naloxone 466-99-9, Hydromorphone 469-62-5, Dextropropoxyphene 469-79-4, Ketobemidone 530-78-9, Flufenamic acid 555-57-7, Pargyline 644-62-2, Meclofenamic acid 655-05-0, Thozalinone 726-99-8, Fluorofelbamate 739-71-9, Trimipramine 768-94-5, Amantadine 853-34-9, Kebuzone 915-30-0, Diphenoxylate 938-73-8, Ethenzamide 1668-19-5, Doxepin 1977-11-3, Perlapine 2210-63-1, Mofebutazone 3286-46-2, Sulbutiamine 3362-45-6, Noxiptilin 4317-14-0, Amitriptylin oxide 4394-00-7, Niflumic acid 4498-32-2, Dibenzepin 4757-55-5, Dimetacrine 5104-49-4, Flurbiprofen 5118-29-6, Melitracen 5560-72-5, Iprindole 6740-88-1, Ketamine 6829-98-7, Imipramine N-oxide 7439-93-2, Lithium, biological studies 10262-69-8, Maprotiline 10321-12-7, Propizepine 13669-70-0, Nefopam 14028-44-5, Amoxapine 14521-96-1, Etorphine 15301-93-6, Tofenacin 15307-86-5, Diclofenac 15574-96-6, Pizotyline 15676-16-1, Sulpiride 15687-27-1, Ibuprofen 17780-72-2, Clorgyline 18464-39-6, Caroxazone 19794-93-5, Trazodone 19982-08-2, Memantine 20290-10-2, Morphine -6-glucuronide 20594-83-6, Nalbuphine 21730-16-5, Metapramine 22071-15-4, Ketoprofen 22204-53-1, Naproxen 22345-47-7, Tofisopam 22494-42-4, Diflunisal 23047-25-8, Lofepramine 23651-95-8, Droxidopa 24219-97-4, Mianserin 24305-27-9, Thyroliberin 24526-64-5, Nomifensine 24701-51-7, Demexiptiline 25451-15-4, Felbamate 25905-77-5, Minaprine 26171-23-3, Tolmetin 26629-87-8, Oxaflozane 27203-92-5, Tramadol 28721-07-5, Oxcarbazepine 29218-27-7, Toloxatone 29679-58-1, Fenoprofen 29975-16-4, Estazolam 30223-48-4, Fluacizine 30544-47-9, Etofenamate 31721-17-2, Quinupramine 32359-34-5, Medifoxamine 33005-95-7, Tiaprofenic acid 34552-84-6, Isoxicam 34911-55-2, Bupropion 35764-73-9, Fluotracen 35941-65-2, Butriptyline 36322-90-4, Piroxicam 37115-32-5, Adinazolam 38194-50-2, Sulindac 40828-46-4, Suprofen 41717-30-0, Befuraline 42408-82-2, Butorphanol 42924-53-8, Nabumetone 46817-91-8, Viloxazine 51022-73-2, Zometapine 51248-68-1 51931-66-9, Tilidine 52463-83-9, Pinazepam 52485-79-7, Buprenorphine 52942-31-1, Etoperidone 53164-05-9, Acemetacin 53179-11-6, Loperamide 53648-55-8, Dezocine 53808-88-1, Lonazolac 54188-38-4, Metralindole 54340-58-8, Meptazinol 54403-19-9, Sercloremine 54739-18-3, Fluvoxamine 54739-19-4, Clovoxamine 54910-89-3, Fluoxetine 56030-54-7 56775-88-3, Zimelidine 56995-20-1, Flupirtine 57262-94-9, Setiptiline 57574-09-1, Amineptine 57982-78-2, Budipine 59729-33-8, Citalopram 59804-37-4, Tenoxicam 59859-58-4, Femoxetine 60142-96-3, Gabapentin 60662-16-0, Binodaline 60719-82-6, Alaproclate 60762-57-4, Pirlindole 60929-23-9, Indeloxazine 61413-54-5, Rolipram 61869-08-7, Paroxetine 62305-86-6, Orotirelin 62473-79-4, Teniloxazine 63638-91-5, Brofaromine 63758-79-2, Indalpine 65165-99-3 66532-85-2,

Propacetamol 66644-81-3, Veralipride 66834-24-0, Cianopramine 67469-69-6, Vanoxerine 67765-04-2, Enefexine 68134-81-6, Gacyclidine 70374-39-9, Lornoxicam 71125-38-7, Meloxicam 71195-58-9, Alfentanyl 71320-77-9, Moclobemide 71620-89-8, Reboxetine 71827-56-0, Clemeprol 72714-74-0, Viqualine 72797-41-2, Tianeptine 73815-11-9, Cimoxatone 74103-06-3, Ketorolac 75991-50-3, Dazepinil 76496-68-9, Levoprotiline 77518-07-1, Amiflamine 78113-47-0 79467-22-4, Bipenamol 79617-96-2, Sertraline 79944-58-4, Idazoxan 80018-06-0, Fengabine 80410-36-2, Fezolamine 83015-26-3, Atomoxetine 83366-66-9, Nefazodone 83891-03-6, Norfluoxetine 84057-84-1, Lamotrigine 85650-52-8, Mirtazapine 86811-09-8, Litoxetine 87051-43-2, Ritanserin 89875-86-5, Tiflucarbine 90243-66-6, Montirelin 90293-01-9, Bifemelane 92623-85-3, Milnacipran 93413-69-5, Venlafaxine 93438-65-4, Conantokin G 94011-82-2, Bazinaprine 96206-92-7, 2-Methyl-6-(phenylethynyl)pyridine 97205-34-0, Nebracetam 97240-79-4, Topiramate 103628-46-2, Sumatriptan 104054-27-5, Atipamezole 104454-71-9, Ipenoxazone 106650-56-0, Sibutramine 112922-55-1, Cericlamine 112924-45-5, Dexanabinol 116539-59-4, Duloxetine 117414-74-1, Midafotel 117571-54-7 120667-19-8 121679-13-8, Naratriptan 123653-11-2, N-[2-(Cyclohexyloxy)-4-nitrophenyl]methanesulfonamide 128196-01-0, Escitalopram 128298-28-2, Remacemide 132472-31-2, (3E)-2-Amino-4-(phosphonomethyl)-3-heptenoic acid 132875-61-7, Remifentanyl 134564-82-2, Befloxatone 135025-56-8, 7-Chlorothiokynurenic acid 137159-92-3, Aptiganel 137433-06-8, (3S,4AR,6S,8aR)-decahydro-6-(phosphonomethyl)-3-isoquinolinecarboxylic acid 138047-56-0, (3R,4S)-rel-3,4-Dihydro-3-[4-hydroxy-4-(phenylmethyl)-1-piperidinyl]-2H-1-benzopyran-4,7-diol 139051-78-8, (2R,4S)-rel-5,7-Dichloro-1,2,3,4-tetrahydro-4-[[(phenylamino)carbonyl]amino]-2-quinolinecarboxylic acid 139264-17-8, Zolmitriptan 143322-58-1, Eletriptan 143850-75-3 144034-80-0, Rizatriptan 144912-63-0 149756-73-0, FPL-12495 150812-12-7, Retigabine
(codrug; preparation of indole compds. and methods for treating visceral pain and other conditions mediated by NOS or 5HT1D/1B receptors)

IT 57-27-2, Morphine, biological studies
(tolerance to and as codrug; preparation of indole compds. and methods for treating visceral pain and other conditions mediated by NOS or 5HT1D/1B receptors)

L8 ANSWER 6 OF 14 USPATFULL on STN

ACCESSION NUMBER: 2009:145908 USPATFULL

TITLE: 3,5 - SUBSTITUTED INDOLE COMPOUNDS HAVING NOS AND NOREPINEPHRINE REUPTAKE INHIBITORY ACTIVITY

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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . Thus from a clinical standpoint, polypharmacy (combining several drugs with different mechanism of action) remains the choice for treatment of neuropathic pain (Wallace, Curr Pain Headache Rep. 2007, 11(3) 208-14). Examples of such combinations include coadministrations of opioids and NSAIDS (e.g., ibuprofen. . .

SUMM . . . selective dual acting nNOS inhibitor/norepinephrine reuptake inhibitor is expected to provide superior efficacy for the treatment of depression and chronic neuropathic pain syndromes. The rationale for a single drug with this dual mechanism action stems from preclinical animal data that have shown. . .

SUMM . . . of chronic pain, in particular visceral pains, osteoarthritis, degenerative spondylosis, lower back pain, painful temporomandibular disorder, fibromyalgia, glossodynia, chemotherapy induced neuropathic pain (e.g., following treatment of breast cancer), postherpetic neuralgia, orthopaedic pain, or medication overuse headache. Exemplary types of visceral pain include. . .

SUMM . . . invention include migraine headache (with or without aura), chronic tension type headache (CTTH), chronic daily headache, migraine with allodynia, epilepsy, neuropathic pain, post-stroke pain, chronic headache, chronic pain, acute spinal cord injury, diabetic neuropathy, trigeminal neuralgia, diabetic nephropathy, an inflammatory disease, stroke,. . . neurological damage, HCA, AIDS associated dementia, neurotoxicity, Parkinson's disease, Alzheimer's disease, ALS, Huntington's disease, multiple sclerosis, metamphetamine-induced neurotoxicity, drug addiction, morphine /opioid induced tolerance, dependence, hyperalgesia, or withdrawal, ethanol tolerance, dependence, or withdrawal, anxiety, depression, unipolar depression, attention deficit hyperactivity disorder, and. . .

SUMM . . . invention

Class	Examples
Opioid	alfentanil, butorphanol, buprenorphine, codeine, dextromoramide, dextropropoxyphene, dezocine, dihydrocodeine, diphenoxylate, etorphine, fentanyl, hydrocodone, hydromorphone, ketobemidone, levorphanol, levomethadone, methadone, meptazinol, morphine, morphine-6-glucuronide, nalbuphine, naloxone,

oxycodone,
oxymorphone, pentazocine, pethidine, piritramide,
remifentanil,
sulfentanyl, tilidine, tramadol, or tapentadol
Antidepressant citalopram, escitalopram, fluoxetine, fluvoxamine,
paroxetine, or
(selective sertraline
serotonin. . . sibutramine, sulbutiamine, sulpiride, teniloxazine,
thozalinone,
thymoliberin, tianeptine, tiflucarbine, trazodone,
tofenacin,
tofisopam, toloxatone, tomoxetine, veralipride,
viloxazine, viqualine,
zimelidine, or zometapine
Antiepileptic carbamazepine, flupirtine, gabapentin,
lamotrigine, levetiracetam,
oxcarbazepine, phenytoin, pregabalin, retigabine,
topiramate, or
valproate
Non-steroidal acemetacin, aspirin, celecoxib, deracoxib, diclofenac,
diflunisal,
anti- ethenzamide, etofenamate, etoricoxib, fenoprofen,. . .
budipine; conantokin G;
aspartate delucemine; dexanabinol; dextromethorphan;
antagonist dextropropoxyphen; felbamate; fluorofelbamate;
gacyclidine; glycine;
ipenoxazone; kaitocephalin; ketamine; ketobemidone;
lanicemine;
licostinel; midafotel; memantine; D-methadone; D-
morphine;
milnacipran; neramexane; orphenadrine; remacemide;
sulfazocine;
FPL-12,495 (racemide metabolite); topiramate;
(αR)-α-amino-5-
chloro-1-(phosphonomethyl)-1H-benzimidazole-2-propanoic
acid; 1-
aminocyclopentane-carboxylic acid;
[5-(aminomethyl)-2-[[[(5S)-9-
chloro-2,3,6,7-tetrahydro-2,3-dioxo-1H-,5H-pyrido[1,2,3-
de]quinoxalin-5-yl]acetyl]amino]phenoxy]-acetic acid;
α-amino-2-
. . .

DRWD FIG. 1a shows the protocol for testing mechanical allodynia in the Chung neuropathic pain model. The L5/L6 spinal nerve was surgically ligated and animals allowed to recover for a period of 7-10 days. During this period animals develop neuropathic pain. The reduction of tactile thresholds (post-SNL) was measured following the induction period for comparison with pre-surgery baseline levels (BL). Following. . .

DRWD FIG. 1b shows the protocol for testing thermal hyperalgesia in the Chung neuropathic pain model. The L5/L6 spinal nerve was surgically ligated and animals allowed to recover for a period of 7-10 days. During this period animals develop neuropathic pain. The reduction of paw withdrawal latency after an infrared thermal stimulus (post-SNL) was measured following the induction period for comparison. . .

DRWD . . . thermal hyperalgesia in rats after i.p. administration of compound (+)-7a (30 mg/kg) in the L5/L6 spinal nerve ligation model of neuropathic pain (Chung model).

DETD . . . containing them, and their medical use, particularly as compounds for the treatment of migraine (acute or prophylaxis), migraine with allodynia, neuropathic pain, post-stroke pain, chronic pain, and depression.

DETD . . . of chronic pain, in particular visceral pains, osteoarthritis, degenerative spondylosis, lower back pain, painful temporomandibular disorder, fibromyalgia, glossodynia, chemotherapy induced neuropathic pain (e.g., following treatment of breast cancer), postherpetic neuralgia, orthopaedic pain, or medication overuse headache. The compounds of the invention may. . .

DETD . . . the invention include migraine headache (with or without aura), migraine prophylaxis, chronic tension type headache (CTTH), migraine with allodynia, epilepsy, neuropathic pain, post-stroke pain, chronic headache, chronic pain, acute spinal cord injury, diabetic neuropathy, trigeminal neuralgia, diabetic nephropathy, an inflammatory disease, stroke,. . . neurological damage, HCA, AIDS associated dementia, neurotoxicity, Parkinson's disease, Alzheimer's disease, ALS, Huntington's disease, multiple sclerosis, metamphetamine-induced neurotoxicity, drug addiction, morphine /opioid induced tolerance, dependence, hyperalgesia, or withdrawal, ethanol tolerance, dependence, or withdrawal, anxiety, depression, attention deficit hyperactivity disorder, and psychosis.

DETD Acute Spinal Cord Injury, Chronic or Neuropathic Pain

DETD . . . (Neuroscience 50(1):7-10, 1992). Thus the NOS inhibitors of the present invention may be useful for the treatment of chronic or neuropathic pain.

DETD Clinical treatment of neuropathic pain with antidepressants is well known. Studies suggest that the reuptake of norepinephrine is the most important property in the mechanism of action involved in neuropathic pain (Max et. al. N. Engl. J. Med 1992, 326, 1250-56; Fishbain et. al. Pain Med. 2000, 1, 310-16; Staiger et.. . . 2540-45). Thus both mechanisms of action in a single molecule are expected to be more effective for treating chronic or neuropathic pain states.

DETD . . . an NOS inhibitor and N-methyl-D-aspartate (NMDA) channel antagonist. Agmatine is effective in both the spinal nerve ligation (SNL) model of neuropathic pain as well as the streptozotocin model of diabetic neuropathy (Karadag et al., Neurosci. Lett. 339(1):88-90, 2003). Given that selective norepinephrine. . . diabetic neuropathy, we believe that a dual acting nNOS/norepinephrine reuptake inhibitor would be effective in treating diabetic neuropathy and other neuropathic pain conditions.

DETD The efficacy of the compounds of the invention for the treatment of neuropathic pain was assessed using standard animal models predictive of anti-hyperalgesic and anti-allodynic activity induced by a variety of methods, each described. . .

DETD (a) Chung Model of Injury-induced Neuropathic-like Pain: The experimental designs for the Chung Spinal Nerve Ligation SNL Model assay for neuropathic pain are depicted in FIGS. 1a and 1b. Nerve ligation injury was performed according to the method described by Kim and. . .

DETD . . . (see FIGS. 3 and 5, respectively). A pronounced antiallodynic effect was observed for 7a was shown in this model of

neuropathic pain.

IT 50-24-8, Prednisolone 50-33-9, Phenylbutazone, biological studies 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-78-2, Aspirin 51-12-7, Nialamide 51-71-8, Phenelzine 52-52-8, 1-Aminocyclopentanecarboxylic acid 53-06-5, Cortisone 53-86-1, Indomethacin 54-92-2, Iproniazid 56-40-6, Glycine, biological studies 57-41-0, Phenytoin 57-42-1, Meperidine 59-63-2, Isocarboxazid 61-68-7, Mefenamic acid 62-44-2, Phenidin 65-45-2, Salicylamide 68-89-3, Metamizol 72-69-5 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 77-07-6, Levorphanol 83-98-7, OrPhenadrine 99-66-1 108-01-0, Deanol 113-53-1, Dothiepin 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 125-58-6, Levomethadone 125-71-3, Dextromethorphan 129-20-4, Oxyphenbutazone 155-09-9, Tranylcypromine 298-46-4, Carbamazepine 302-41-0, Piritramide 303-48-0, Norclomipramine 303-49-1, Clomipramine 315-72-0, Opipramol 357-56-2, Dextromoramide 359-83-1, Pentazocine 437-38-7, Fentanyl 438-60-8, Protriptyline 465-65-6, Naloxone 466-99-9, Hydromorphone 469-62-5, Dextropropoxyphene 469-79-4, Ketobemidone 479-92-5, Propyphenazone 530-78-9, Flufenamic acid 555-57-7, Pargyline 644-62-2, Meclofenamic acid 655-05-0, Thozalinone 726-99-8, Fluorofelbamate 739-71-9, Trimipramine 768-94-5, Amantadine 853-34-9, Kebuzone 915-30-0, Diphenoxylate 938-73-8, Ethenzamide 1668-19-5, Doxepin 1977-11-3, Perlapine 2210-63-1, Mofebutazone 3286-46-2, Sulbutiamine 3362-45-6, Noxiptilin 4317-14-0, Amitriptyline oxide 4394-00-7, Niflumic acid 4498-32-2, Dibenzepin 4757-55-5, Dimetacrine 5104-49-4, Flurbiprofen 5118-29-6, Melitracen 5560-72-5, Iprindole 6740-88-1, Ketamine 6829-98-7, Imipramine N-oxide 7439-93-2, Lithium, biological studies 10262-69-8, Maprotiline 10321-12-7, Propizepine 13669-70-0, Nefopam 14028-44-5, Amoxapine 14521-96-1, Etorphine 15301-93-6, Tofenacin 15307-86-5, Diclofenac 15574-96-6, Pizotyline 15676-16-1, Sulpiride 15687-27-1, Ibuprofen 17780-72-2, Clorgyline 18464-39-6, Caroxazone 19794-93-5, Trazodone 19982-08-2, Memantine 20290-10-2, Morphine -6-glucuronide 20594-83-6, Nalbuphine 21730-16-5, Metapramine 22071-15-4, Ketoprofen 22204-53-1, Naproxen 22345-47-7, Tofisopam 22494-42-4, Diflunisal 23047-25-8, Lofepramine 23651-95-8, Droxidopa 24219-97-4, Mianserin 24305-27-9, Thyroliberin 24526-64-5, Nomifensine 24701-51-7, Demexiptiline 25451-15-4, Felbamate 25905-77-5, Minaprine 26171-23-3, Tolmetin 26629-87-8, Oxaflozane 27203-92-5, Tramadol 28721-07-5, Oxcarbazepine 29218-27-7, Toloxatone 29679-58-1, Fenoprofen 29975-16-4, Estazolam 30223-48-4 30544-47-9, Etofenamate 31721-17-2, Quinupramine 32359-34-5, Medifoxamine 33005-95-7, Tiaprofenic acid 34552-84-6, Isoxicam 34911-55-2, Bupropion 35764-73-9, Fluotracen 35941-65-2, Butriptyline 36322-90-4, Piroxicam 37115-32-5, Adinazolam 38194-50-2, Sulindac 40828-46-4, Suprofen 41717-30-0, Befuraline 42408-82-2, Butorphanol 42924-53-8, Nabumetone 46817-91-8, Viloxazine 51022-73-2, Zometapine 51248-68-1 51931-66-9, Tilidine 52463-83-9, Pinazepam 52485-79-7, Buprenorphine 52942-31-1, Etoperidone 53164-05-9, Acemetacin 53179-11-6, Loperamide 53648-55-8, Dezocine 53808-88-1, Lonazolac 54188-38-4 54403-19-9 54739-18-3, Fluvoxamine 54739-19-4, Clovoxamine 54910-89-3, Fluoxetine 56030-54-7 56775-88-3, Zimelidine 56995-20-1, Flupirtine 57262-94-9, Setiptiline 57574-09-1, Amineptine 57982-78-2, Budipine 59729-33-8, Citalopram 59804-37-4, Tenoxicam 59859-58-4, Femoxetine 60142-96-3, Gabapentin 60662-16-0 60719-82-6, Alaproclate 60762-57-4,

Pirlindole 60929-23-9, Indeloxazine 61413-54-5, Rolipram 61869-08-7, Paroxetine 62305-86-6 62473-79-4, Teniloxazine 63638-91-5, Brofaromine 63758-79-2, Indalpine 66532-85-2, Propacetamol 66644-81-3, Veralipride 66834-24-0, Cianopramine 67469-69-6, Vanoxerine 67765-04-2 68134-81-6, Gacyclidine 70374-39-9, Lornoxicam 71125-38-7, Meloxicam 71195-58-9, Alfentanyl 71320-77-9, Moclobemide 71620-89-8, Reboxetine 71827-56-0, Clemeprol 72714-74-0, Viqualine 72797-41-2, Tianeptine 73815-11-9, Cimoxatone 74103-06-3, Ketorolac 75991-50-3, Dazepinil 76496-68-9, Levoprotiline 77518-07-1, Amiflamine 79467-22-4, Bipenamol 79617-96-2, Sertraline 79944-58-4, Idazoxan 80018-06-0, Fengabine 80410-36-2 83015-26-3, Atomoxetine 83366-66-9, Nefazodone 83891-03-6, Norfluoxetine 84057-84-1, Lamotrigine 85650-52-8, Mirtazapine 86811-09-8, Litoxetine 87051-43-2, Ritanserin 89875-86-5, Tiflucarbine 90243-66-6, Montirelin 90293-01-9, Bifemelane 92623-85-3, Milnacipran 93413-69-5, Venlafaxine 93438-65-4, Conantokin G 94011-82-2, Bazinaprine 96206-92-7, 2-Methyl-6-(phenylethynyl)pyridine 97205-34-0, Nebracetam 97240-79-4, Topiramate 103628-46-2, Sumatriptan 104054-27-5, Atipamezole 104454-71-9, Ipenoxazone 106650-56-0, Sibutramine 112922-55-1, Cericlamine 112924-45-5, Dexanabinol 116539-59-4, Duloxetine 117414-74-1, Midafotel 117571-54-7 120667-19-8 121679-13-8, Naratriptan 123653-11-2, N-[2-(Cyclohexyloxy)-4-nitrophenyl]methanesulfonamide 128196-01-0, Escitalopram 128298-28-2, Remacemide 132472-31-2, (3E)-2-Amino-4-(phosphonomethyl)-3-heptenoic acid 132875-61-7, Remifentanyl 134564-82-2, Befloxatone 135025-56-8, 7-Chlorothiokynurenic acid 137159-92-3, Aptiganel 137433-06-8, (3S,4AR,6S,8aR)-decahydro-6-(phosphonomethyl)-3-isoquinolinecarboxylic acid 138047-56-0, (3R,4S)-rel-3,4-Dihydro-3-[4-hydroxy-4-(phenylmethyl)-1-piperidinyl]-2H-1-benzopyran-4,7-diol 139051-78-8, (2R,4S)-rel-5,7-Dichloro-1,2,3,4-tetrahydro-4-[[(phenylamino)carbonyl]amino]-2-quinolinecarboxylic acid 139264-17-8, Zolmitriptan 142235-88-9, 3-(Phosphonomethyl)-L-phenylalanine 143322-58-1, Eletriptan 143850-75-3 144034-80-0, Rizatriptan 144912-63-0 149756-73-0 150812-12-7, Retigabine 153322-05-5, Lanicemine
(codrug; preparation of 3,5-substituted indole compds. having NOS and norepinephrine reuptake inhibitory activity for treating pain, psychiatric disorders, and other diseases)

IT 57-27-2, Morphine, biological studies
(tolerance to and as codrug; preparation of 3,5-substituted indole compds. having NOS and norepinephrine reuptake inhibitory activity for treating pain, psychiatric disorders, and other diseases)

L8 ANSWER 7 OF 14 CA COPYRIGHT 2010 ACS on STN DUPLICATE 5
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REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Combination methods and compositions for treatment of neuropathic pain

AB The present invention relates generally to the field of pain management, and in particular, the management of neuropathic pain.

The present invention further provides methods and compns. that treat, alleviate, prevent, diminish or otherwise ameliorate the symptoms of neuropathic pain without inducing overt sedation. The present invention also contemplates combination therapy using one or more NK antagonists in combination with. . .

SYSTEM LIMIT EXCEEDED DURING KWIC/STRING SEARCH

ST analgesic combination neuropathic pain therapy NK1 antagonist

IT Burkitt lymphoma
(African type; combination methods and compns. for treatment of neuropathic pain)

IT Bone, disease
(Albright's syndrome; combination methods and compns. for treatment of neuropathic pain)

IT Ulcer
(Barrett's; combination methods and compns. for treatment of neuropathic pain)

IT Spinal cord
(GABAa receptors; combination methods and compns. for treatment of neuropathic pain)

IT GABA receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GABAA, spinal cord; combination methods and compns. for treatment of neuropathic pain)

IT Tachykinin antagonists
(NK1 receptor antagonists; combination methods and compns. for treatment of neuropathic pain)

IT Tachykinin antagonists
(NK3 receptor antagonists; combination methods and compns. for treatment of neuropathic pain)

IT Transient receptor potential cation channel TRPV

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TRPV1, modulators; combination methods and compns. for treatment of neuropathic pain)
IT Bone, disease
(achondroplasia, tarda; combination methods and compns. for treatment of neuropathic pain)
IT Bone, disease
(achondroplasia; combination methods and compns. for treatment of neuropathic pain)
IT Dwarfism
(achondroplastic, tarda; combination methods and compns. for treatment of neuropathic pain)
IT Dwarfism
(achondroplastic; combination methods and compns. for treatment of neuropathic pain)
IT Porphyria
(acute intermittent; combination methods and compns. for treatment of neuropathic pain)
IT Skin, disease
(acute toxic epidermolysis; combination methods and compns. for treatment of neuropathic pain)
IT Porphyria
(acute; combination methods and compns. for treatment of neuropathic pain)
IT Disease, animal
(adiposis dolorosa; combination methods and compns. for treatment of neuropathic pain)
IT Adrenoleukodystrophy
(adrenomyeloneuropathy; combination methods and compns. for treatment of neuropathic pain)
IT Dermatomyositis
(adult; combination methods and compns. for treatment of neuropathic pain)
IT Stenosis
(anal; combination methods and compns. for treatment of neuropathic pain)
IT Neoplasm
(angioma, cavernous; combination methods and compns. for treatment of neuropathic pain)
IT Meningitis
(arachnoiditis, chronic adhesive; combination methods and compns. for treatment of neuropathic pain)
IT Meningitis
(arachnoiditis, ossificans; combination methods and compns. for treatment of neuropathic pain)
IT Meningitis
(arachnoiditis, postmyelog.; combination methods and compns. for treatment of neuropathic pain)
IT Meningitis
(arachnoiditis, spinal; combination methods and compns. for treatment of neuropathic pain)
IT Meningitis
(arachnoiditis; combination methods and compns. for treatment of neuropathic pain)
IT Amides
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(arylcyclopropylcarboxylic and 3-(pyridinyl-piperazin-1-yl)-phenylethyl; combination methods and compns. for treatment of neuropathic pain)
IT Paralysis
(ascending; combination methods and compns. for treatment of neuropathic pain)
IT Neuroglia, neoplasm
(astrocytoma, grade I and II (benign); combination methods and compns. for treatment of neuropathic pain)
IT Dermatitis
(atopic; combination methods and compns. for treatment of neuropathic pain)
IT Brain, neoplasm
Central nervous system, neoplasm
(benign; combination methods and compns. for treatment of neuropathic pain)
IT Ischemia
(brachiocephalic; combination methods and compns. for treatment of neuropathic pain)
IT Skin, disease
(bullous pemphigoid; combination methods and compns. for treatment of neuropathic pain)
IT Skin, disease
(bullous; combination methods and compns. for treatment of neuropathic pain)
IT Neurofibromatosis
(central form; combination methods and compns. for treatment of neuropathic pain)
IT Movement disorders
(cerebral palsy, athetoid; combination methods and compns. for treatment of neuropathic pain)
IT Dermatomyositis
(childhood; combination methods and compns. for treatment of neuropathic pain)
IT Bone, disease
(chondrodysplasia, punctata; combination methods and compns. for treatment of neuropathic pain)
IT Connective tissue disease
(chondrodystrophia calcificans congenita; combination methods and compns. for treatment of neuropathic pain)
IT Myotonia
(chondrodystrophic; combination methods and compns. for treatment of neuropathic pain)
IT AIDS (disease)
Adrenal gland, neoplasm
Amyotrophic lateral sclerosis
Amyotrophic lateral sclerosis
Analgesics
Arachnitis
Arthritis
Autonomic neuropathy
Barrett esophagus
Beriberi
Bone neoplasm
Brain, neoplasm

Burkitt lymphoma
Calcium channel blockers
Charcot-Marie-Tooth disease
Charcot-Marie-Tooth disease
Charcot-Marie-Tooth disease
Combination chemotherapy
Controlled-release drug delivery systems
Crohn disease
Demyelination
Dermatomyositis
Ellis-van Creveld syndrome
Endometriosis
Fibromyalgia
Fibromyalgia
Fragile X syndrome
Guillain-Barre syndrome
Guillain-Barre syndrome
Hodgkin's disease
Hodgkin's disease
Human
Lupus erythematosus
Mammalia
Multiple myeloma
Multiple sclerosis
Multiple sclerosis
NMDA receptor antagonists
Nonsteroidal anti-inflammatory drugs
Polymyalgia rheumatica
Potassium channel openers
Psoriasis
Scleroderma
Sedation
Sickle cell anemia
Sodium channel blockers
Systemic lupus erythematosis
Thalassemia
Varicella
(combination methods and compns. for treatment of neuropathic pain)

IT Opioids
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination methods and compns. for treatment of neuropathic pain)

IT Pain
(complex regional pain syndrome; combination methods and compns. for treatment of neuropathic pain)

IT Spinal cord disease
(congenital tethered cervical; combination methods and compns. for treatment of neuropathic pain)

IT Arteritis
(cranial; combination methods and compns. for treatment of neuropathic pain)

IT Carcinoma
(cutaneous squamous cell; combination methods and compns. for treatment of neuropathic pain)

IT Porphyria
(cutaneous; combination methods and compns. for treatment of neuropathic pain)
IT Stenosis
(degenerative lumbar spinal; combination methods and compns. for treatment of neuropathic pain)
IT Cutaneous lupus erythematosus
(discoid; combination methods and compns. for treatment of neuropathic pain)
IT Reticuloendothelial system
(disease, histiocytosis, polyostotic sclerosing; combination methods and compns. for treatment of neuropathic pain)
IT Cartilage formation
(disorders; combination methods and compns. for treatment of neuropathic pain)
IT Connective tissue disease
(eosinophilic fasciitis; combination methods and compns. for treatment of neuropathic pain)
IT Skin, disease
(epidermolysis bullosa; combination methods and compns. for treatment of neuropathic pain)
IT Keratosis
Keratosis
Keratosis
(epidermolytic hyperkeratosis; combination methods and compns. for treatment of neuropathic pain)
IT Skin, disease
(erythroderma, congenital ichthyosiform; combination methods and compns. for treatment of neuropathic pain)
IT Neuron
(excitation; combination methods and compns. for treatment of neuropathic pain)
IT Lymphatic system
(familiallymphedema praecox; combination methods and compns. for treatment of neuropathic pain)
IT Disease, animal
(generalized fibromatosis; combination methods and compns. for treatment of neuropathic pain)
IT Arteritis
Arteritis
Arteritis
Arteritis
(giant cell arteritis; combination methods and compns. for treatment of neuropathic pain)
IT Disease, animal
(hemangiomatosis chondrodystrophica; combination methods and compns. for treatment of neuropathic pain)
IT Disease, animal
(histiocytosis, polyostotic sclerosing; combination methods and compns. for treatment of neuropathic pain)
IT Myelination
(hypomyelination, congenital; combination methods and compns. for treatment of neuropathic pain)
IT Skin, disease
(ichthyosis, bullous; combination methods and compns. for treatment of neuropathic pain)

IT Cartilage formation
(imperfecta; combination methods and compns. for treatment of neuropathic pain)
IT Diabetes mellitus
Diabetes mellitus
(insulin-dependent; combination methods and compns. for treatment of neuropathic pain)
IT Skin, disease
(juvenile dermatomyositis; combination methods and compns. for treatment of neuropathic pain)
IT Rheumatoid arthritis
Rheumatoid arthritis
(juvenile; combination methods and compns. for treatment of neuropathic pain)
IT Ulcer
(leg; combination methods and compns. for treatment of neuropathic pain)
IT Anesthetics
(local; combination methods and compns. for treatment of neuropathic pain)
IT Anus
Rectum
(malformation; combination methods and compns. for treatment of neuropathic pain)
IT Headache
(migraine, abdominal; combination methods and compns. for treatment of neuropathic pain)
IT GABA receptors
α2-Adrenoceptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(modulators; combination methods and compns. for treatment of neuropathic pain)
IT Hemangioma
(multiple cavernous; combination methods and compns. for treatment of neuropathic pain)
IT Edema
Hypothyroidism
(myxedema, Addison's disease; combination methods and compns. for treatment of neuropathic pain)
IT Addison's disease
(myxedema; combination methods and compns. for treatment of neuropathic pain)
IT Astrocyte
(neoplasm, astrocytoma, grade I and II (benign); combination methods and compns. for treatment of neuropathic pain)
IT Inflammation
Nerve, disease
(neuritis, acute shoulder; combination methods and compns. for treatment of neuropathic pain)
IT Inflammation
Nerve, disease
(neuritis, brachial; combination methods and compns. for treatment of neuropathic pain)
IT Inflammation
Nerve, disease
(neuritis, chronic idiopathic polyneuritis; combination methods and

compns. for treatment of neuropathic pain)
IT Inflammation
Nerve, disease
(neuritis, peripheral; combination methods and compns. for treatment of neuropathic pain)
IT Pain
(neuropathic pain; combination methods and compns. for treatment of neuropathic pain)
IT Amyloidosis
(neuropathic; combination methods and compns. for treatment of neuropathic pain)
IT Nerve, disease
(neuropathy, brachial-plexus; combination methods and compns. for treatment of neuropathic pain)
IT Nerve, disease
(neuropathy, onion-bulb; combination methods and compns. for treatment of neuropathic pain)
IT Nerve, disease
(neuropathy; combination methods and compns. for treatment of neuropathic pain)
IT Burkitt lymphoma
(non-African type; combination methods and compns. for treatment of neuropathic pain)
IT Diabetes mellitus
(non-insulin-dependent; combination methods and compns. for treatment of neuropathic pain)
IT Herpes
(ocular; combination methods and compns. for treatment of neuropathic pain)
IT Alkaloids
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opium, hydrochlorides; combination methods and compns. for treatment of neuropathic pain)
IT Bone, disease
(osteogenesis imperfecta congenita; combination methods and compns. for treatment of neuropathic pain)
IT Bone, disease
(osteogenesis imperfecta tarda; combination methods and compns. for treatment of neuropathic pain)
IT Bone, disease
Bone, disease
(osteogenesis imperfecta; combination methods and compns. for treatment of neuropathic pain)
IT Arteritis
Inflammation
(polyarteritis nodosa; combination methods and compns. for treatment of neuropathic pain)
IT Myositis
(polymyositis; combination methods and compns. for treatment of neuropathic pain)
IT Nerve, disease
(polyneuropathy, chronic inflammatory demyelinating; combination methods and compns. for treatment of neuropathic pain
)
IT Tripeptides

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(possersi; combination methods and compns. for treatment of neuropathic pain)
IT Multiple sclerosis
(primary progressive; combination methods and compns. for treatment of neuropathic pain)
IT Spinal column, disease
(spina bifida; combination methods and compns. for treatment of neuropathic pain)
IT Stenosis
(spinal, cervical; combination methods and compns. for treatment of neuropathic pain)
IT Stenosis
(spinal; combination methods and compns. for treatment of neuropathic pain)
IT Skin, neoplasm
(squamous cell carcinoma; combination methods and compns. for treatment of neuropathic pain)
IT Drug interactions
(synergistic; combination methods and compns. for treatment of neuropathic pain)
IT Nerve, disease
Pain
(trigeminal neuralgia; combination methods and compns. for treatment of neuropathic pain)
IT Cannabinoid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type CB2, modulators; combination methods and compns. for treatment of neuropathic pain)
IT Tachykinin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type NK1, agonists, phosphorylated morpholine acetal; combination methods and compns. for treatment of neuropathic pain
)
IT Capsaicin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type VR1, modulators; combination methods and compns. for treatment of neuropathic pain)
IT Leg, disease
(ulcer; combination methods and compns. for treatment of neuropathic pain)
IT Arthritis
(urethritica; combination methods and compns. for treatment of neuropathic pain)
IT Porphyria
(variegata; combination methods and compns. for treatment of neuropathic pain)
IT Spinal column
(vertebra, cervical vertebral fusion; combination methods and compns. for treatment of neuropathic pain)
IT Hyperostosis
(vertebral ankylosing; combination methods and compns. for treatment of neuropathic pain)
IT Abdomen
(wall defect; combination methods and compns. for treatment of

neuropathic pain)
IT 182822-62-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CP 141938; combination methods and compns. for treatment of neuropathic pain)
IT 216776-73-7
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CS 003; combination methods and compns. for treatment of neuropathic pain)
IT 136565-66-7
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ES 242-1; combination methods and compns. for treatment of neuropathic pain)
IT 60559-94-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(P 1060; combination methods and compns. for treatment of neuropathic pain)
IT 120667-19-8
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(PD 129635; combination methods and compns. for treatment of neuropathic pain)
IT 272104-60-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(SB 414240; combination methods and compns. for treatment of neuropathic pain)
IT 173941-22-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(YM 35375; combination methods and compns. for treatment of neuropathic pain)
IT 9004-65-3, Hydroxypropylmethyl cellulose
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination methods and compns. for treatment of neuropathic pain)
IT 50-76-0D, Actinomycin D, analogs 50-78-2, Aspirin 53-86-1, Indomethacin 54-21-7, Sodium salicylate 55-21-0D, Benzamide, N-[(R,R)-(E)-1-arylmethyl-3-(2-oxo-azepin-3-yl)carbamoyl]allyl-N-methy-3,5-bis(triflurомethyl)- derivs. 57-27-2, Morphine, biological studies 57-42-1, Pethidine 58-00-4, Apomorphine 58-74-2, Papaverine 59-46-1, Procaine 61-68-7, Relafan 72-19-5, Threonine, biological studies 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 77-10-1, Phencyclidine 91-19-0D, Quinoxaline, imidazo[4,5-b] derivs. 91-22-5D, Quinoline, derivs. 103-90-2, Acetaminophen 110-85-0D, Piperazine, diacyl derivs. 110-86-1D, Pyridine, achiral derivs. 110-89-4D, Piperidine, 1-alkyl-5-(3,4-dichlorophenyl)-5-[2-[(3-substituted)-1-azetidinyl]ethyl]-2- derivs. 110-89-4D, Piperidine, 4-alkyl derivative 110-89-4D, Piperidine, spiro-substituted derivs. 110-91-8D, Morpholine, phosphorylated acetal derivs. 111-40-0, Diethylenetriamine 125-28-0, Dihydrocodeine

125-71-3, Dextromethorphan 125-73-5, Dextrorphan 128-62-1, Noscapine 136-47-0 137-58-6, Lignocaine 312-84-5, D-Serine 357-56-2, Dextromoramide 359-83-1, Pentazocine 364-98-7, Diazoxide 404-86-4, Capsaicin 427-00-9, Desomorphine 437-38-7, Fentanyl 466-90-0, Dihydrocodeinone enol acetate 466-99-9, Hydromorphone 469-62-5, Dextropropoxyphene 492-27-3, Kynurenic acid 504-24-5, 4-Aminopyridine 509-60-4, Dihydromorphine 552-94-3, Salsalate 561-27-3, Diamorphine 598-41-4, Glycinamide 646-25-3, 1,10-Diaminodecane 768-94-5, Amantadine 1003-51-6, HA 966 1218-34-4 1744-22-5, Riluzole 2016-36-6 2379-57-9, DNQX) 2782-40-3D, Butylbenzamide, 4-Amino-2-(aryl)- derivs. 2783-17-7, 1,12-Diaminododecane 4741-41-7, Dexoxadrol 6238-14-8, 3-Aminoquinuclidine 6385-02-0, Meclomen 6740-88-1, Ketamine 10238-21-8, Glyburide 14107-37-0, Alphadolone 14176-49-9, Tiletamine 14198-28-8, SKF10047 15307-86-5, Diclofenac 15687-27-1, Ibuprofen 18000-24-3, 7-Chloro-kynurenic acid 18917-89-0, Magan 19982-08-2, Memantine 21256-18-8, Oxaprozin 21500-98-1, TCP 22071-15-4, Ketoprofen 22204-53-1, Naproxen 23187-87-3, Triasate 23210-56-2, Ifenprodil 25451-15-4, Felbamate 26171-23-3, Tolmetin 27203-92-5, Tramadol 31828-71-4, Mexiletine 31842-01-0, Indoprofen 33005-95-7, Tiaprofenic acid 33041-33-7D, Pregnanedione, analogs 33507-63-0, Substance P 36322-90-4, Piroxicam 38194-50-2, Sulindac 38304-91-5, Minoxidil 38396-39-3, Bupivacaine 42924-53-8, Nabumetone 51165-07-2, Substance P-(6-11) 51803-78-2, Nimesulide 52485-79-7, Buprenorphine 53749-60-3, Substance P-(4-11) 56995-20-1, Flupirtine 60560-33-0, Pinacidil 65141-46-0, Nicorandil 70374-27-5, Lomoxicam 71125-38-7, Meloxicam 71195-58-9, Alfentanil 72909-34-3, PQQ 74103-07-4, Ketorolac tromethamine 76326-31-3, AP5 77086-21-6, Dizocilpine 77275-70-8 78660-92-1D, analogs 79775-19-2, Septide 80062-77-7 80434-86-2 80937-31-1, Flosulide 84057-84-1, Lamotrigine 84057-95-4, Ropivacaine 84676-91-5 85797-13-3, AP7 91224-37-2, Spantide I 94421-68-8, Anandamide 94470-67-4, Cromakalim 94535-50-9, Levcromakalim 95372-93-3, PD 137889 95751-30-7, Charybdotoxin 97559-38-1 100828-16-8, CPP 101238-51-1, Levemopamil 106128-89-6, Senktide 106883-96-9D, derivs. 107025-80-9, E2001 110347-85-8, CGS19755 112924-45-5, HU-211) 115066-14-3, CNQX 116049-53-7, CGP40116 117414-74-1, D-CPP-ene) 118077-09-1, SDZEAB515 119431-25-3, Eliprodil 122063-01-8, (β-Ala(8))-Neurokinin A (4-10) 124916-54-7, Celikalim 125546-04-5, LY233053 125652-47-3, CGP31358 125787-94-2, FK224 125989-12-0, L659877 125989-15-3, L 659874 126050-12-2, MEN 10207 126088-92-4, FR113680 126088-92-4D, FR113680, derivs. 127493-01-0, GR71251 127910-32-1, CGP39551 128298-28-2, Remacemide 129176-97-2, Spantide II 129623-01-4, GR82334 129781-07-3, MEN 10208 129809-09-2, R396 129938-34-7, MDL 100453 131123-76-7, 5,7-Dichlorokynurenic acid 132014-88-1, CPP-ene 132453-03-3, PD138289 132746-60-2, CP-96345 133156-06-6, GR73632 135306-85-3, MEN10376 135911-02-3, RP67580 136109-04-1, LY274614 136845-59-5, LY233536 136982-36-0, CP 99994 137012-28-3, L 668169 137159-92-3, Aptiganel 137593-52-3, GR64349 138449-07-7, FK888 138738-21-3, MDL100925 138977-28-3, Capsazepine 140202-46-6, SC48981 140202-48-8, PD145950 141636-44-4, GR 83074 141636-65-9, GR 98400 142001-63-6, SR48968 142923-40-8, LY235723 143153-94-0 144177-30-0, WIN 51708 144301-37-1, NPC17742 144425-84-3, L703606 145194-26-9, Sendide 145742-28-5, CP 122721 146362-70-1, SR48692 147116-64-1, Ezlopitant 147145-55-9, L 161664 147696-46-6, ZD6169 148451-96-1, L 732138 148700-85-0, L733060 148700-91-8, L733061 149250-10-2, S16474 150705-88-7, CGP 49823 150812-12-7, Retigabine 150881-27-9, WIN 64821

151911-03-4, MEN 10573 152269-54-0 153438-49-4, RPR100893
154427-06-2, Spantide III 155418-05-6, SR 140333 155418-06-7,
Nolpitantium besilate 157351-81-0, MEN 10627 158574-85-7
158991-23-2, PD 154075 159706-39-5, L742694 160492-56-8, Osanetant
164178-33-0, AM630 167261-60-1, MDL 105212A 168266-90-8, GR205171
168273-06-1, SR141716 168398-02-5, GR 203040 169340-04-9, ZM253270
170566-84-4, Lanepitant 170567-08-5, LY306740 170729-80-3, MK 869
171752-63-9, ZD 7944 172081-08-2, TAC 363 172673-20-0, L758298
173050-51-6, SR142801 173941-74-7, YM 44778 174635-69-9, SB222200
174636-32-9, Talnetant 174769-78-9, S18523 177476-74-3, WAY-133537
177707-12-9, NK 608 178309-91-6, UK 224671 180046-99-5, SDZNKT343
182621-58-5 183673-27-0, HSP 117 183747-35-5, Nepadutant
187523-35-9, BMS-204352 188241-50-1, S19752 192703-06-3, SR144528
201152-86-5, SR 144190 204519-66-4, SB223412A 206052-25-7, MEN 11149
211689-03-1, MEN11558 214487-46-4, MEN 11467 215036-24-1, L 760735
217185-75-6, TAK 637 224961-34-6, SB 235375
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(combination methods and compns. for treatment of neuropathic
pain)

IT 235093-18-2, MDL 103392 262598-99-2 263860-84-0, ZD 4974
264618-44-2, SSR 146977 265121-04-8, MK 0517 279215-43-9, NN414
290297-26-6, Netupitant 311340-66-6, R 673 334476-46-9, Vestipitant
334476-64-1, GW 597599 350610-29-6, ZM 274773 350610-51-4, CGP 60829
350610-64-9, NKP 608C 393183-40-9 398507-81-8, DNK333 403993-96-4,
MEN13510 414910-27-3, Casopitant 439915-37-4, YM 38336 439915-39-6,
Sch 205528 439915-40-9, Sch 62373 439915-41-0, R 113281 500019-57-8,
PD 138558 501951-42-4, SB 705498 537034-22-3, SSR 240600
627907-13-5D, analogs 661467-08-9, UK 290795 793639-30-2, PD 132477
808145-40-6, SLV 323 847158-60-5, NIK 616 852393-14-7, GW 679769
852393-17-0, GW 823296 875322-32-0, FK 355 875322-37-5, NIP 530
875322-45-5, AVE 5883 891501-12-5, SSR 241586 947517-38-6, TA 5538
947517-40-0, MPC 4505 947517-68-2, AV 608 1000615-17-7, NK 5807
1013028-34-6 1013028-35-7 1095714-82-1 1095714-83-2 1095714-84-3
1095714-85-4 1095714-86-5D, 2-substituted-4-aryl- derivs.
1095714-87-6D, 9-substituted-7-aryl- derivs. 1095714-88-7D,
9-substituted-7-aryl- derivs. 1095714-89-8 1095714-90-1D, derivs.
1096099-07-8 1096153-45-5, CP 9634 1096153-72-8, S 18525
1096153-79-5, WIN 51703 1096153-82-0, SB 40023 1096153-85-3, AZ 311
1096153-87-5, SB 733210 1096153-89-7, AZ 685 1096153-93-3, SAR 102279
1096153-94-4, SLV 332 1096153-95-5, MPV 4505 1096153-96-6, Z 501
(pharmaceutical) 1096154-00-5, S 18920 1096154-02-7, HMR 2091
1096154-05-0, NIP 531 1096154-07-2, AZD 5106 1096154-08-3, SDZPC 0400
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(combination methods and compns. for treatment of neuropathic
pain

L8 ANSWER 8 OF 14 CA COPYRIGHT 2010 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 149:402219 CA
TITLE: Preparation of tetrahydroquinolines and related compounds having NOS inhibitory activity
INVENTOR(S): Maddaford, Shawn; Ramnauth, Jailall; Rakhit, Suman; Patman, Joanne; Annedi, Subhash C.; Andrews, John; Dove, Peter; Silverman, Sarah; Renton, Paul
PATENT ASSIGNEE(S): Neuraxon, Inc., Can.

10574438

SOURCE: U.S. Pat. Appl. Publ., 148 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20080234237	A1	20080925	US 2008-54083	20080324
AU 2008232269	A1	20081002	AU 2008-232269	20080325
CA 2681771	A1	20081002	CA 2008-2681771	20080325
WO 2008116308	A1	20081002	WO 2008-CA569	20080325
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
EP 2139886	A1	20100106	EP 2008-748081	20080325
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR				

PRIORITY APPLN. INFO.: US 2007-896829P P 20070323
WO 2008-CA569 W 20080325

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 149:402219

IT Pain
(neuropathic pain, chemotherapy-induced; preparation of tetrahydroquinolines and related compds. having NOS inhibitory activity)

IT Pain
(neuropathic pain; preparation of tetrahydroquinolines and related compds. having NOS inhibitory activity)

IT 57-27-2, Morphine, biological studies 57-42-1, Pethidine 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 77-07-6, Levorphanol 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 125-58-6, Levomethadone 302-41-0, Piritramide 357-56-2, Dextromoramide 359-83-1, Pentazocine 437-38-7, Fentanyl 465-65-6, Naloxone 466-99-9, Hydromorphone 469-62-5, Propoxyphene 915-30-0, Diphenoxylate 14521-96-1, Etorphine 20290-10-2, Morphine -6-glucuronide 20594-83-6, Nalbuphine 27203-92-5, Tramadol 42408-82-2, Butorphanol 51931-66-9, Tilidine 52485-79-7, Buprenorphine 53179-11-6, Loperamide 53648-55-8, Dezocine 54340-58-8, Meptazinol 56030-54-7 71195-58-9, Alfentanyl 132875-61-7, Remifentanyl
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of tetrahydroquinolines and related compds. having NOS inhibitory activity)

IT 50-24-8, Prednisolone 50-33-9, Phenylbutazone, biological studies

50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-52-2, Thioridazine 50-53-3, biological studies 50-78-2, Aspirin 51-12-7, Nialamide 51-71-8, Phenelzine 52-52-8, 1-Aminocyclopentane-carboxylic acid 52-86-8, Haloperidol 53-06-5, Cortisone 53-86-1, Indomethacin 54-92-2, Iproniazide 56-40-6, Glycine, biological studies 58-25-3, Chlorodiazepoxide 58-38-8, Prochlorperazine 58-39-9, Perphenazine 58-40-2, Promazine 59-63-2, Isocarboxazide 59-92-7, Levodopa, biological studies 60-99-1, Methotrimeprazine 61-68-7, Mefenamic acid 62-44-2, Phenidin 65-45-2, Salicylamide 68-35-9, Sulfazine 68-89-3, Metamizol 69-23-8, Fluphenazine 72-69-5, Nortriptyline 83-98-7, Orphenadrine 99-66-1 103-90-2, Acetaminophen 108-01-0, Deanol 113-53-1, Dothiepin 113-59-7, Chlorprothixene 117-89-5, Trifluoperazine 125-71-3, Dextromethorphan 129-20-4, Oxyphenbutazone 155-09-9, Tranylcypromine 298-46-4, Carbamazepine 303-48-0, Norclomipramine 303-49-1, Clomipramine 315-72-0, Opipramol 438-60-8, Protriptyline 469-79-4, Ketobemidone 479-92-5, Propyphenazone 530-78-9, Flufenamic acid 548-73-2, Droperidol 555-57-7, Pargyline 630-93-3 644-62-2, Meclofenamic acid 655-05-0, Thozalinone 726-99-8, Fluorofelbamate 739-71-9, Trimipramine 739-71-9D, Trimipramine, derivs. 768-94-5, Amantadine 853-34-9, Kebuzone 938-73-8, Ethenzamide 1668-19-5, Doxepin 1977-10-2, Loxapine 1977-11-3, Perlapine 2062-78-4, Pimozide 2210-63-1, Mofebutazone 2709-56-0, Flupenthixol 2751-68-0, Acetophenazine 3286-46-2, Sulbutiamine 3313-26-6, Thiothixene 3362-45-6, Noxiptilin 4317-14-0, Amitriptylin oxide 4394-00-7, Niflumic acid 4498-32-2, Dibenzepin 4757-55-5, Dimetacrine 5104-49-4, Flurbiprofen 5118-29-6, Melitracen 5560-72-5, Iprindole 5588-33-0, Mesoridazine 5653-80-5 5786-21-0, Clozapine 6740-88-1, Ketamine 6829-98-7, Imipramin oxide 7416-34-4, Molindone 7439-93-2, Lithium, biological studies 10262-69-8, Maprotiline 10321-12-7, Propizepine 13669-70-0, Nefopam 14028-44-5, Amoxapine 15301-93-6, Tofenacin 15307-86-5, Diclofenac 15574-96-6, Pizotyline 15676-16-1, Sulpiride 15687-27-1, Ibuprofen 17780-72-2, Clorgyline 18464-39-6, Caroxazone 19794-93-5, Trazodone 19982-08-2, Memantine 21730-16-5, Metapramine 22071-15-4, Ketoprofen 22204-53-1, Naproxen 22345-47-7, Tofisopam 22494-42-4, Diflunisal 23047-25-8, Lofepramine 23651-95-8, Droxidopa 24219-97-4, Mianserin 24305-27-9, Thyroliberin 24526-64-5, Nomifensine 24701-51-7, Demexiptiline 25451-15-4, Felbamate 25905-77-5, Minaprine 26171-23-3, Tolmetin 26629-87-8, Oxaflozane 28721-07-5, Oxcarbazepine 29218-27-7, Toloxatone 29679-58-1, Fenoprofen 29975-16-4, Estazolam 30223-48-4 30544-47-9, Etofenamate 31721-17-2, Quinupramine 32359-34-5, Medifoxamine 33005-95-7, Tiaprofenic acid 34552-84-6, Isoxicam 34911-55-2, Bupropion 35764-73-9, Fluotracen 35941-65-2, Butriptyline 36322-90-4, Piroxicam 37115-32-5, Adinazolam 38194-50-2, Sulindac 39860-99-6, Pipotiazine 40828-46-4, Suprofen 41717-30-0, Befuraline 42924-53-8, Nabumetone 46817-91-8, Viloxazine 51022-73-2, Zometapine 52463-83-9, Pinazepam 52942-31-1, Etoperidone 53164-05-9, Acemetacin 53808-88-1, Lonazolac 54188-38-4 54403-19-9 54739-18-3, Fluvoxamine 54739-19-4, Clovoxamine 54910-89-3, Fluoxetine 56775-88-3, Zimelidine 56995-20-1, Flupirtine 57262-94-9, Setiptiline 57574-09-1, Amineptine 57982-78-2, Budipine 59729-33-8, Citalopram 59804-37-4, Tenoxicam 59859-58-4, Femoxetine 60142-96-3, Gabapentin 60662-16-0 60719-82-6, Alaproclate 60762-57-4, Pirlindole 60929-23-9, Indeloxazine 61413-54-5, Rolipram 61869-08-7, Paroxetine 62305-86-6 62473-79-4, Teniloxazine 63638-91-5, Brofaromine

63758-79-2, Indalpine 66532-85-2, Propacetamol 66644-81-3, Veralipride
66834-24-0, Cianopramine 67469-69-6, Vanoxerine 67765-04-2
68134-81-6, Gacyclidine 70374-39-9, Lornoxicam 71125-38-7, Meloxicam
71320-77-9, Moclobemide 71620-89-8, Reboxetine 71827-56-0, Clemeprol
72714-74-0, Viqualine 72797-41-2, Tianeptine 73815-11-9, Cimoxatone
74103-06-3, Ketorolac 75991-50-3, Dazepinil 76496-68-9, Levoprotiline
77518-07-1, Amiflamine 79467-22-4, Bipenamol 79617-96-2, Sertraline
79944-58-4, Idazoxan 80018-06-0, Fengabine 80410-36-2 83015-26-3,
Atomoxetine 83366-66-9, Nefazodone 83891-03-6, Norfluoxetine
84057-84-1, Lamotrigine 85650-52-8, 6-Aza-mianserin 86811-09-8,
Litoxetine 87051-43-2, Ritanserin 89875-86-5, Tiflucarbine
90243-66-6, Montirelin 90293-01-9, Bifemelane 92623-85-3, Milnacipran
93413-69-5, Venlafaxine 93438-65-4, Conantokin G 94011-82-2,
Bazinaprine 96206-92-7, 2-Methyl-6-(phenylethynyl)pyridine 97205-34-0,
Nebracetam 97240-79-4, Topiramate 103628-46-2, Sumatriptan
104054-27-5, Atipamezole 104454-71-9, Ipenoxazone 104632-26-0,
Pramipexole 106266-06-2, Risperidone 106516-24-9, Sertindole
106650-56-0, Sibutramine 111974-69-7, Quetiapine 112922-55-1,
Cericlamine 112924-45-5, Dexanabinol 116539-59-4, Duloxetine
117414-74-1, Midafotel 117571-54-7 120667-19-8 121679-13-8,
Naratriptan 123653-11-2 128196-01-0, Escitalopram 128298-28-2,
Remacemide 129722-12-9, Aripiprazole 132472-31-2,
(3E)-2-Amino-4-(phosphonomethyl)-3-heptenoic acid 132539-06-1,
Olanzapine 133454-47-4, Iloperidone 134564-82-2, Befloxatone
135025-56-8, 7-Chlorothiokynurenic acid 137159-92-3, Aptiganel
137433-06-8, (3S,4AR,6S,8aR)-decahydro-6-(phosphonomethyl)-3-
isoquinolinecarboxylic acid 138047-56-0,
(3R,4S)-rel-3,4-Dihydro-3-[4-hydroxy-4-(phenylmethyl)-1-piperidinyl]-2H-1-
benzopyran-4,7-diol 139051-78-8,
(2R,4S)-rel-5,7-Dichloro-1,2,3,4-tetrahydro-4-
[[(phenylamino)carbonyl]amino]-2-quinolinecarboxylic acid 139264-17-8,
Zolmitriptan 142235-88-9 143322-58-1, Eletriptan 143850-75-3
144034-80-0, Rizatriptan 144912-63-0 146939-27-7, Ziprasidone
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(preparation of tetrahydroquinolines and related compds. having NOS
inhibitory activity)

L8 ANSWER 9 OF 14 USPATFULL on STN
ACCESSION NUMBER: 2008:284441 USPATFULL
TITLE: SUBSTITUTED INDOLE COMPOUNDS HAVING NOS INHIBITORY ACTIVITY
INVENTOR(S): Maddaford, Shawn, Mississauga, CANADA
Ramnauth, Jailall, Brampton, CANADA
Rakhit, Suman, Mississauga, CANADA
Patman, Joanne, Mississauga, CANADA
Renton, Paul, Toronto, CANADA
Annedi, Subhash C., Mississauga, CANADA
PATENT ASSIGNEE(S): NeurAxon Inc., Toronto, CANADA (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20080249302	A1	20081009
APPLICATION INFO.:	US 2008-47963	A1	20080313 (12)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2006-404267, filed on 13 Apr 2006, Pat. No. US 7375219

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-670856P	20050413 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	CLARK & ELBING LLP, 101 FEDERAL STREET, BOSTON, MA, 02110, US	
NUMBER OF CLAIMS:	12	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	23 Drawing Page(s)	
LINE COUNT:	6319	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

RLI Continuation of Ser. No. US 2006-404267, filed on 13 Apr 2006, Pat. No. US 7375219

AB . . . stroke, reperfusion injury, neurodegeneration, head trauma, CABG, migraine headache with and without aura, migraine with allodynia, central post-stroke pain (CPSP), neuropathic pain, morphine/opioid induced tolerance and hyperalgesia.

SUMM . . . artery bypass graft (CABG) associated neurological damage, migraine with and without aura, migraine with allodynia, chronic tension type headache (CTTH), neuropathic pain, post-stroke pain, and chronic pain.

SUMM . . . can be prevented or treated include migraine headache (with or without aura), chronic tension type headache (CTTH), migraine with allodynia, neuropathic pain, post-stroke pain, chronic headache, chronic pain, acute spinal cord injury, diabetic neuropathy, trigeminal neuralgia, diabetic nephropathy, an inflammatory disease, stroke,. . . . neurological damage, HCA, AIDS associated dementia, neurotoxicity, Parkinson's disease, Alzheimer's disease, ALS, Huntington's disease, multiple sclerosis, metamphetamine-induced neurotoxicity, drug addiction, morphine/opioid induced tolerance, dependence, hyperalgesia, or withdrawal, ethanol tolerance, dependence, or withdrawal, epilepsy, anxiety, depression, attention deficit hyperactivity disorder, and psychosis.. . . neurodegeneration, head trauma, CABG associated neurological damage, migraine headache (with or without aura), migraine with allodynia, chronic tension type headache, neuropathic pain, post-stroke pain, opioid induced hyperalgesia, or chronic pain. In particular, 3,5-substituted indole compounds are useful for treating migraine, with or. . .

SUMM . . . invention

Class	Examples
Opioid	alfentanil, butorphanol, buprenorphine, codeine, dextromoramide, dextropropoxyphene, dezocine, dihydrocodeine, diphenoxylate, etorphine, fentanyl, hydrocodone, hydromorphone, ketobemidone, levorphanol, levomethadone, methadone, meptazinol, morphine, morphine-6-glucuronide, nalbuphine, naloxone, oxycodone, oxymorphone, pentazocine, pethidine, piritramide,

remifentanil,
sulfentanyl, tilidine, or tramadol
Antidepressant (selective serotonin reuptake inhibitor) citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline
Antidepressant. . . sibutramine, sulbutiamine, sulpiride, teniloxazine, thozalinone,
thymoliberin, tianeptine, tiflucarbine, trazodone, tofenacin,
tofisopam, toloxatone, tomoxetine, veralipride, viloxazine, viqualine,
zimelidine, or zometapine
Antiepileptic carbamazepine, flupirtine, gabapentin, lamotrigine, oxcarbazepine,
phenyloin, retigabine, topiramate, or valproate
Non-steroidal anti-inflammatory. . . acemetacin, aspirin, celecoxib, deracoxib, diclofenac, diflunisal,
ethenzamide, etofenamate, etoricoxib, fenoprofen, flufenamic acid,
budipine; conantokin G;
aspartate antagonist delucemine; dexanabinol; dextromethorphan;
dextropropoxyphen; felbamate; fluorofelbamate; gacyclidine; glycine;
ipenoxazone; kaitocephalin; ketamine; ketobemidone; lanicemine;
licostinel; midafotel; memantine; D-methadone; D-morphine;
milnacipran; neramexane; orphenadrine; remacemide; sulfazocine;
FPL-12,495 (racemide metabolite); topiramate;
(αR)-α-amino-5-chloro-1-(phosphonomethyl)-1H-benzimidazole-2-propanoic acid; 1-aminocyclopentane-carboxylic acid;
[5-(aminomethyl)-2-[[[(5S)-9-chloro-2,3,6,7-tetrahydro-2,3-dioxo-1H-,5H-pyrido[1,2,3-de]quinoxalin-5-yl]acetyl]amino]phenoxy]-acetic acid;
α-amino-2-
. . .
DRWD . . . of the experimental designs used in the Chung Spinal Nerve Ligation (SNL) model assays (tactile allodynia and thermal hyperalgesia) for neuropathic pain.
DRWD . . . administration of compounds 32(+) and 32(−) on the reversal of thermal hyperalgesia in rats after L5/L6 spinal nerve ligation (Chung neuropathic pain model).
DRWD . . . administration of compounds 32(+) and 32(−) on the reversal of tactile allodynia in rats after L5/L6 spinal nerve ligation (Chung neuropathic pain model).
DRWD . . . (3 mg/kg-30 mg/kg) of compound 12 on the reversal of thermal hyperalgesia in rats after L5/L6 spinal nerve ligation (Chung neuropathic pain model).
DRWD . . . (3 mg/kg-30 mg/kg) of compound 12 on the reversal of tactile hyperthesia in rats after L5/L6 spinal nerve ligation (Chung neuropathic pain model).

DETD . . . of stroke, reperfusion injury, neurodegenerative disorders, head trauma, coronary artery bypass graft (CABG) associated neurological damage, migraine, migraine with allodynia, neuropathic pain, post-stroke pain, and chronic pain.

DETD . . . a cell or animal in need thereof. Such diseases or conditions include, for example, migraine headache with and without aura, neuropathic pain, chronic tension type headache headache, chronic pain, acute spinal cord injury, diabetic neuropathy, diabetic nephropathy, an inflammatory disease, stroke, reperfusion. . . neurological damage, HCA, AIDS associated dementia, neurotoxicity, Parkinson's disease, Alzheimer's disease, ALS, Huntington's disease, multiple sclerosis, metamphetamine-induced neurotoxicity, drug addiction, morphine/opioid induced tolerance, dependence, hyperalgesia or withdrawal, ethanol tolerance, dependence, or withdrawal, epilepsy, anxiety, depression, attention deficit hyperactivity disorder, and psychosis.. . .

DETD Acute Spinal Cord Injury, Chronic or Neuropathic Pain

DETD . . . (Neuroscience 50(1):7-10, 1992). Thus the NOS inhibitors of the present invention may be useful for the treatment of chronic or neuropathic pain.

DETD . . . an NOS inhibitor and N-methyl-D-aspartate (NMDA) channel antagonist. Agmatine is effective in both the spinal nerve ligation (SNL) model of neuropathic pain well as the streptozotocin model of diabetic neuropathy (Karadag et al., Neurosci. Lett. 39(1):88-90, 2003). Thus compounds possessing NOS inhibitory. . . I, a combination of an NOS inhibitor and an NMDA antagonist should be effective in treating diabetic neuropathy and other neuropathic pain conditions.

DETD (b) Morphine/Opioid Induced Tolerance and Withdrawal Symptoms

DETD . . . both the NMDA and NO pathways in opioid dependence in adult and infant animals. Adult or neonatal rodents injected with morphine sulfate develop behavioral withdrawal after precipitation with naltrexone. The withdrawal symptoms after naltrexone initiation can be reduced by administration of. . . 150(3):325-336, 2000). In a related study, it was shown that the more nNOS selective inhibitor 7-NI attenuated more of the morphine induced withdrawal symptoms including mastication, salivation and genital effects than the less selective compounds (Vaupel et al., Psychopharmacology (Berl.) 118(4):361-8,. . .

DETD . . . alfentanil, butorphanol, buprenorphine, dextromoramide, dezocine, dextropropoxyphene, codeine, dihydrocodeine, diphenoxylate, etorphine, fentanyl, hydrocodone, hydromorphone, ketobemidone, loperamide, levorphanol, levomethadone, meperidine, meptazinol, methadone, morphine, morphine-6-glucuronide, nalbuphine, naloxone, oxycodone, oxymorphone, pentazocine, pethidine, piritramide, propoxylphene, remifentanil, sulfentanyl, tilidine, and tramadol.

DETD Opioid-NOS Inhibitor Combinations in Chronic, Neuropathic Pain

DETD Nerve injury can lead to abnormal pain states known as neuropathic pain. Some of the clinical symptoms include tactile allodynia (nociceptive responses to normally innocuous mechanical stimuli), hyperalgesia (augmented pain intensity in response to normally painful stimuli), and spontaneous pain. Spinal nerve ligation (SNL) in rats is an animal model of neuropathic pain that produces spontaneous pain, allodynia, and

hyperalgesia, analogous to the clinical symptoms observed in human patients (Kim and Chung, Pain. . .

DETD Neuropathic pain can be particularly insensitive to opioid treatment (Benedetti et al., Pain 74:205-211, 1998) and is still considered to be relatively. . . Pain 16:S49-S55, 2000). While dose escalation can overcome reduced opioid effectiveness, it is limited by increased side effects and tolerance. Morphine administration is known to activate the NOS system, which limits the analgesic action of this drug (Machelska et al., NeuroReport. . . 2000; Xiangqi and Clark, Mol. Brain. Res. 95:96-102, 2001). However, it has been shown that the combined systemic administration of morphine and L-NAME can attenuate mechanical and cold allodynia at subthreshold doses at which neither drug administered alone was effective (Ulugol et al., Neurosci. Res. Com. 30(3):143-153, 2002). The effect of L-NAME co-administration on morphine analgesia appears to be mediated by nNOS, as L-NAME loses its ability to potentiate morphine analgesia in nNOS null-mutant mice (Clark and Xiangqi, Mol. Brain. Res. 95:96-102, 2001). Enhanced analgesia has been demonstrated in the. . .

DETD . . . the combination of an nNOS inhibitor with an opioid (for example, those combinations described above) can enhance opioid analgesia in neuropathic pain and prevent the development of opioid tolerance and opioid-induced hyperalgesia.

DETD Antidepressant-NOS Inhibitor Combinations for Chronic Pain, Neuropathic Pain, Chronic Headache or Migraine

DETD Many antidepressants are used for the treatment of neuropathic pain (McQuay et al., Pain 68:217-227, 1996) and migraine (Tomkins et al., Am. J. Med. 111:54-63, 2001), and act via the. . .

DETD . . . J. Pharmacol. 102:198-202, 1992). Thus, compounds possessing n-NOS inhibitory activity should be effective for the treatment of inflammatory pain and neuropathic pain symptoms of allodynia and hyperalgesia resulting from inflammation.

DETD The efficacy of the compounds of the invention for the treatment of neuropathic pain was assessed using standard animal models predictive of anti-hyperalgesic and anti-allodynic activity induced by a variety of methods, each described. . .

DETD (a) Chung Model of Injury-induced Neuropathic-like Pain: The experimental designs for the Chung Spinal Nerve Ligation SNL Model assay for neuropathic pain are depicted in FIG. 18. Nerve ligation injury was performed according to the method described by Kim and Chung (Kim. . .

DETD . . . 20 and 22, respectively). A clear difference between the two enantiomers of compound 32 was observed in this model of neuropathic pain.

IT 57-27-2, Morphine, biological studies 57-42-1, Meperidine 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 77-07-6, Levorphanol 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 125-58-6, Levomethadone 302-41-0, Piritramide 357-56-2, Dextromoramide 359-83-1, Pentazocine 437-38-7, Fentanyl 465-65-6, Naloxone 466-99-9, Hydromorphone 469-79-4, Ketobemidone 915-30-0, Diphenoxylate 14521-96-1, Etorphine 20290-10-2, Morphine -6-glucuronide 20594-83-6, Nalbuphine 27203-92-5, Tramadol 42408-82-2, Butorphanol 51931-66-9, Tilidine 52485-79-7, Buprenorphine 53179-11-6, Loperamide 53648-55-8, Dezocine 54340-58-8, Meptazinol 56030-54-7 71195-58-9, Alfentanil 132875-61-7, Remifentanil
(preparation of substituted indole compds. with NOS inhibitory activity

useful as therapeutic agents)
IT 50-24-8, Prednisolone 50-33-9, Phenylbutazone, biological studies
50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine
50-78-2, Aspirin 51-12-7, Nialamide 51-71-8, Phenelzine 52-52-8,
1-Aminocyclopentane-carboxylic acid 53-06-5, Cortisone 53-86-1,
Indomethacin 54-92-2, Iproniazid 56-40-6, Glycine, biological studies
58-25-3, Chlordiazepoxide 59-63-2, Isocarboxazid 61-68-7, Mefenamic
acid 62-44-2 65-45-2, Salicylamide 68-89-3, Metamizol 72-69-5,
Nortriptyline 83-98-7, Orphenadrine 99-66-1 108-01-0, Deanol
113-53-1, Dothiepin 125-71-3, Dextromethorphan 129-20-4,
Oxyphenbutazone 155-09-9, Tranylcypromine 298-46-4, Carbamazepine
303-49-1, Clomipramine 315-72-0, Opipramol 438-60-8, Protriptyline
469-62-5, Dextropropoxyphen 479-92-5, Propyphenazone 530-78-9,
Flufenamic acid 555-57-7, Pargyline 630-93-3, Phenyloin 644-62-2,
Meclofenamic acid 655-05-0, Thozalinone 726-99-8 739-71-9,
Trimipramine 768-94-5, Amantadine 853-34-9, Kebuzone 938-73-8,
Ethenzamide 1668-19-5, Doxepin 1977-11-3, Perlapine 2210-63-1,
Mofebutazone 3286-46-2, Sulbutiamine 3362-45-6, Noxiptilin
4394-00-7, Niflumic acid 4498-32-2, Dibenzepin 4757-55-5, Dimetacrine
5104-49-4, Flurbiprofen 5118-29-6, Melitracen 5560-72-5, Iprindole
5653-80-5 6740-88-1, Ketamine 6829-98-7, Imipramine-N-oxide
7439-93-2, Lithium, biological studies 10262-69-8, Maprotiline
10321-12-7, Propizepine 13669-70-0, Nefopam 14028-44-5, Amoxapine
15301-93-6, Tofenacin 15307-86-5, Diclofenac 15574-96-6, Pizotyline
15676-16-1, Sulpiride 15687-27-1, Ibuprofen 17780-72-2, Clorgyline
18464-39-6, Caroxazone 19794-93-5, Trazodone 19982-08-2, Memantine
21730-16-5, Metapramine 22071-15-4, Ketoprofen 22204-53-1, Naproxen
22345-47-7, Tofisopam 22494-42-4, Diflunisal 23047-25-8, Lofepramine
23651-95-8, Droxidopa 24219-97-4, Mianserin 24526-64-5, Nomifensine
24701-51-7, Demexiptiline 25451-15-4, Felbamate 25905-77-5, Minaprine
26171-23-3, Tolmetin 26629-87-8, Oxaflozane 28721-07-5, Oxcarbazepine
29218-27-7, Toloxatone 29679-58-1, Fenoprofen 29975-16-4, Estazolam
30223-48-4 30544-47-9, Etofenamate 31721-17-2, Quinupramine
32359-34-5, Medifoxamine 33005-95-7, Tiaprofenic acid 34552-84-6,
Isoxicam 34911-55-2, Bupropion 35764-73-9, Fluotracen 35941-65-2,
Butriptyline 36322-90-4, Piroxicam 37115-32-5, Adinazolam
38194-50-2, Sulindac 40828-46-4, Suprofen 41717-30-0, Befuraline
42924-53-8, Nabumetone 46817-91-8, Viloxazine 52463-83-9, Pinazepam
52942-31-1, Etoperidone 53164-05-9, Acemetacin 53808-88-1, Lonazolac
54188-38-4 54403-19-9 54739-18-3, Fluvoxamine 54739-19-4,
Clovoxamine 54910-89-3, Fluoxetine 56775-88-3, Zimelidine
56995-20-1, Flupirtine 57262-94-9, Setiptiline
57574-09-1, Amineptine 57982-78-2, Budipine 59729-33-8, Citalopram
59804-37-4, Tenoxicam 59859-58-4, Femoxetine 60142-96-3, Gabapentin
60662-16-0 60719-82-6, Alaproclate 60929-23-9, Indeloxazine
61413-54-5, Rolipram 61869-08-7, Paroxetine 62305-86-6 62473-79-4,
Teniloxazine 63638-91-5, Brofaromine 63758-79-2, Indalpine
65165-99-3 66532-85-2, Propacetamol 66644-81-3, Veralipride
66834-24-0, Cianopramine 67469-69-6, Vanoxerine 67765-04-2
68134-81-6, Gacyclidine 70374-39-9, Lornoxicam 71125-38-7, Meloxicam
71320-77-9, Moclobemide 71620-89-8, Reboxetine 71827-56-0, Clemeprol
72714-74-0, Viqualine 72797-41-2, Tianeptine 73815-11-9, Cimoxatone
74103-06-3, Ketorolac 75991-50-3, Dazepinil 76496-68-9, Levoprotiline
77518-07-1, Amiflamine 79467-22-4, Bipenamol 79617-96-2, Sertraline
79944-58-4, Idazoxan 80018-06-0, Fengabine 80410-36-2 83015-26-3,
Tomoxetine 83366-66-9, Nefazodone 83891-03-6, Norfluoxetine

84057-84-1, Lamotrigine 85650-52-8, 6-Azamianserin 86811-09-8, Litoxetine 87051-43-2, Ritanserin 89875-86-5, Tiflucarbine 90243-66-6, Montirelin 90293-01-9, Bifemelane 92623-85-3, Milnacipran 93413-69-5, Venlafaxine 93438-65-4, Conantokin G 94011-82-2, Bazinaprine 96206-92-7, 2-Methyl-6-(phenylethynyl)-pyridine 97205-34-0, Nebracetam 97240-79-4, Topiramate 103628-46-2, Sumatriptan 104054-27-5, Atipamezole 104454-71-9, Ipenoxazone 106650-56-0, Sibutramine 112922-55-1, Cericlamine 112924-45-5, Dexanabinol 116539-59-4, Duloxetine 117414-74-1, Midafotel 117571-54-7 120667-19-8 121679-13-8, Naratriptan 123653-11-2, N-[2-(Cyclohexyloxy)-4-nitrophenyl]methanesulfonamide 128196-01-0, Escitalopram 128298-28-2, Remacemide 132472-31-2, (3E)-2-Amino-4-(phosphonomethyl)-3-heptenoic acid 134564-82-2, Befloxatone 135025-56-8, 7-Chlorothiokynurenic acid 137159-92-3, Aptiganel 137433-06-8, (3S,4AR,6S,8aR)-decahydro-6-(phosphonomethyl)-3-isoquinolinecarboxylic acid 138047-56-0, (3R,4S)-rel-3,4-Dihydro-3-[4-hydroxy-4-(phenylmethyl)-1-piperidinyl]-2H-1-benzopyran-4,7-diol 139051-78-8, (2R,4S)-rel-5,7-Dichloro-1,2,3,4-tetrahydro-4-[[(phenylamino)carbonyl]amino]-2-quinolinecarboxylic acid 139264-17-8, Zolmitriptan 142235-88-9 143322-58-1, Eletriptan 144034-80-0, Rizatriptan 144912-63-0 149756-73-0 150812-12-7, Retigabine 153322-05-5, Lanicemine 153504-81-5, Licostinel 158747-02-5, Frovatriptan 160754-76-7, N'-[2-Chloro-5-(methylthio)phenyl]-N-methyl-N-[3-(methylthio)phenyl]-guanidine 161230-88-2 162011-90-7, Rofecoxib 166974-22-7 169590-41-4, Deracoxib 169590-42-5, Celecoxib 170029-85-3 173186-99-7 180200-68-4, 4-(4-Cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide 181695-72-7, Valdecoxib 186495-49-8, Delucemine 193278-48-7 193359-26-1, 1-[2-(4-Hydroxyphenoxy)ethyl]-4-[(4-methylphenyl)methyl]-4-piperidinol 197077-52-4, 6,7-Dichloro-1,4-dihydro-5-[3-(methoxymethyl)-5-(3-pyridinyl)-4H-1,2,4-triazol-4-yl]-2,3-quinoxalinedione 198470-84-7, Parecoxib 198559-42-1 198710-92-8, Kaitocephalin 200430-63-3, 1,4-Dihydro-6-methyl-5-[(methylamino)methyl]-7-nitro-2,3-quinoxalinedione 202409-33-4, Etoricoxib 202844-10-8, 2-[(2,3-Dihydro-1H-inden-2-yl)amino]-acetamide 212126-32-4, 2-(3,5-Difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one 213980-27-9 219810-59-0, Neramexane 252374-41-7, 1-[4-(1H-Imidazol-4-yl)-3-butynyl]-4-(phenylmethyl)-piperidine 253450-09-8, Besonprodil 266320-83-6 342047-49-8 369640-27-7, 2-Hydroxy-5-[[(pentafluorophenyl)methyl]amino]-benzoic acid 398479-93-1, M 3-PPC
(preparation of substituted indole compds. with NOS inhibitory activity useful as therapeutic agents)

L8 ANSWER 10 OF 14 USPATFULL on STN
ACCESSION NUMBER: 2008:66442 USPATFULL
TITLE: Novel pharmaceutical compositions for treating chronic pain and pain associated with neuropathy
INVENTOR(S): Singh, Chandra Ulagaraj, San Antonio, TX, UNITED STATES
Woody, David Lloyd, New Braunfels, TX, UNITED STATES
Nulu, Jagaveerabhadra Rao, Austin, TX, UNITED STATES

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	US 7645767	B2	20100112
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LEGAL REPRESENTATIVE: NATHANIEL GORDON-CLARK, 1025 NORTH CALVERT STREET, BALTIMORE, MD, 21202, US
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NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 3156
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . in arteriosclerosis obliterans, stroke, heart attack, and angina pectoris. Cancer is also the cause of significant pain in our society. Neurogenic pain can be due to posttraumatic and postoperative neuralgia. Neurogenic pain also can be related to degenerative neuropathies due to diabetes and can be secondary to a variety of toxic insults. Neurogenic pain can also be due to nerve entrapment, irritation or disruption, facial neuralgia, perineal neuralgia, post-amputation phantom pain, thalamic, causalgia, and. . .

SUMM Neuropathic pain is a common variety of chronic pain. It can be defined as pain that results from an abnormal functioning of. . . the pain known as causalgia, wherein even a light touch to the skin is felt as an excruciating burning pain. Neuropathic pain is thought to be a consequence of damage to peripheral nerves or to regions of the central nervous system. However,. . . as diabetes. Thus, many types of chronic pain related to inflammatory processes can be considered to be at least partly neuropathic pains.

SUMM . . . most frequently used agents for pain control. Opiates are narcotic agonistic analgesics and are drugs derived from opium, such as morphine, codeine, and many synthetic congeners of morphine, with morphine and hydrocodone preparations being the most widely used opiates. Opiates are natural and synthetic drugs with morphine-like actions. Opiates are narcotic agonistic analgesics which produce drug dependence of the morphine type and are subject to control under Federal narcotics law and the laws of most other nations and international organizations. . .

SUMM The chemical classes of opiates with morphine like activity are the purified alkaloids of opium consisting of phenanthrenes and benzylisoquinolines, semi-synthetic derivatives of morphine, phenylpiperidine derivatives, morphinan derivatives, benzomorphan derivatives, diphenyl-heptane derivatives, and propionanilide derivatives. The principal phenanthrenes are morphine, codeine, and thebaine. The principal benzoisoquinolines are papaverine, a smooth muscle relaxant, and noscapine. Semi-synthetic derivatives of morphine include diacetylmorphine (heroin), hydromorphone, oxymorphone, hydrocodone, apomorphine, etorpine, and oxycodone. Phenylpiperidine derivatives include meperidine and its congeners diphenoxylate and loperamide,. . .

SUMM In addition to the μ-opiate receptor agonists such as

morphine, other classes of analgesic agents that are commonly used include agonistic-antagonistic analgesic agents, non-steroidal anti-inflammatory drugs (NSAIDS), steroids, cyclooxygenase inhibitors,. . .

SUMM . . . decreases proportionately with the diminished analgesic activity of the higher doses. Agonistic-antagonistic analgesic agents with pharmacological activity similar to the morphine like opiates include pentazocine, nalbuphine, butorphanol, nalorphine, buprenorphine (a partial agonist), meptazinol, dezocine, and cyclazocine.

SUMM . . . is adjusted to provide the level of pain relief comparable to that achieved by the administration of five milligrams of morphine administered intramuscularly.

SUMM For example, the withdrawal of morphine, heroin, or other μ-opiate agonists with similar durations of action from an individual dependent upon the opiate gives rise to. . . pupils, anorexia, gooseflesh, restlessness, irritability, and tremor. At the peak intensity of withdrawal, which is 48 to 72 hours for morphine and heroin, the individual suffers from increasing irritability, insomnia, marked anorexia, violent yawning, severe sneezing, lacrimation, coryzia, feelings of weakness,. . . which, when combined with the vomiting, sweating, and diarrhea, results in weight loss, dehydration, and ketosis. The withdrawal symptoms from morphine and heroin usually disappear in 7 to 10 days, but the drug dependent individual suffers greatly during the withdrawal period.. . . intensity within 30 minutes, with a more severe withdrawal than that caused by simply withholding the opiate. Withdrawal of other morphine like opiates will produce the same or similar withdrawal symptoms, with the intensity of the symptoms dependent upon the duration of action of the morphine opiate.

SUMM . . . in the individual merely substituting one opiate dependency for another. In the case of individuals dependent upon opiates such as morphine or heroin, methadone, an opiate with morphine -like activity, is given to the drug dependent individual on a daily basis in a rigidly controlled regimen. The methadone suppresses. . . the euphoric effects of all opiates, but if the methadone is abruptly withdrawn, withdrawal symptoms similar to those caused by morphine restriction will appear, albeit of lower intensity but which are of longer duration.

SUMM . . . used. In general, the SSRI's have not been found to be as effective as the TCA's for the treatment of neuropathic pain, but are better tolerated. The side effects of the SSRI's include sweating, stomach upset, somnolence, dizziness, decreased libido, and ejaculatory. . .

SUMM . . . or alleviating the development of constipation or other symptoms of intestinal hypomotility wherein an opiate analgesic or antitussive such as morphine, meperidine, oxycodone, hydromorphone, codeine and hydrocodone is administered to the patient together with an opiate antagonist such as naloxone, naloxone. . .

SUMM Other approaches to the treatment of chronic pain and neuropathic pain have included the administration of a pharmaceutically acceptable acid addition salt or a protonated derivative of at least one microtubule. . .

SUMM . . . al, 1993), diabetic neuropathy (Capsaicin Study Group, 1992), postmastectomy pain syndrome (Watson and Evans, 1992; Dini et al, 1993), oral neuropathic pain, trigeminal neuralgia, and

temperomandibular joint disorders (Epstein and Marcoe, 1994; Hersh et al, 1994), cluster headache (following intranasal application) (Marks. . .

SUMM . . . regional anesthesia, and this produced sustained analgesia lasting 1 to 8 weeks in cases of complex regional pain syndrome and neuropathic pain (Robbins et al, 1998). When topical local anesthetics were applied with 1% topical capsaicin, no alteration in pain produced by. . .

SUMM . . . a concentration from greater than about 5% to about 10% by weight to be an extremely effective therapy for treating neuropathic pain, so long as an anesthetic, preferably by means of a transdermal patch, is administered initially to the affected area to. . .

SUMM . . . the present invention, a NMDA receptor antagonist can be dextromethorphan, dextrorphan, ketamine, amantadine, memantine, eliprodil, ifenprodil, phencyclidine, MK-801, dizocilpine, CCPene, flupirtine, or derivatives or salts thereof.

DETD . . . control strategies has focused on the N-methyl-D-aspartate (NMDA) receptors and their antagonists which were recently shown to alleviate somatic and neuropathic pain sensation in both animal and human models (Plesan et al, 1998, Klepstad et al, 1990, Eisenberg et al, 1998, Kinnman. . .

DETD Dextromethorphan and levorphanol were originally synthesized as pharmacological alternatives to morphine more than 40 years ago. DM is the D isomer of the codeine analogue, levorphanol but, in contrast to its. . .

DETD . . . more convenient than the other anti-NMDA drugs, all of which are administered by injection, such as ketamine. As a potential morphine sparing agent for pain, the use of DM was shown to be efficient and well tolerated (Henderson et al, 1999).

DETD . . . of the debrisoquine-type, cytochrome P450 2D6 (CYP2D6). One mechanism relates to its weak affinity for μ-opiate receptors (6,000-fold less than morphine, 100-fold less than d-propoxyphene, 10-fold less than codeine, and equivalent to dextromethorphan). Moreover, and in contrast to other opiates, the. . .

DETD . . . al, 1993), diabetic neuropathy (Capsaicin Study Group, 1992), postmastectomy pain syndrome (Watson and Evans, 1992; Dini et al, 1993), oral neuropathic pain, trigeminal neuralgia, and temperomandibular joint disorders (Epstein and Marcoe, 1994; Hersh et al, 1994), cluster headache (following intranasal application) (Marks. . .

DETD . . . regional anesthesia, and this produced sustained analgesia lasting 1 to 8 weeks in cases of complex regional pain syndrome and neuropathic pain (Robbins et al, 1998). When topical local anesthetics were applied with 1% topical capsaicin, no alteration in pain produced by. . .

DETD . . . which may be utilized in the present invention include dextromethorphan, dextrorphan, ketamine, amantadine, memantine, eliprodil, ifenprodil, phencyclidine, MK-801, dizocilpine, CCPene, flupirtine, or derivatives, salts, metabolites or complexes thereof.

CLM What is claimed is:

. . . composition of claim 1, wherein the NMDA antagonist is dextromethorphan, dextrorphan, ketamine, amantadine, memantine, eliprodil, ifenprodil, phencyclidine, MK-801, dizocilpine, CCPene,

flupirtine, or derivatives or salts thereof.

CLM What is claimed is:
. . . composition of claim 2, wherein the NMDA antagonist is dextromethorphan, dextrorphan, ketamine, amantadine, memantine, eliprodil, ifenprodil, phencyclidine, MK-801, dizocilpine, CCPene, flupirtine, or derivatives or salts thereof.

IT 77-10-1, Phencyclidine 125-71-3, Dextromethorphan 125-73-5, Dextrorphan 137-66-6, Ascorbyl palmitate 768-94-5, Amantadine 2444-46-4, Nonivamide 2444-46-4D, Nonivamide, derivs. 6740-88-1, Ketamine 18609-21-7, Dextromethorphan hydrochloride 19408-84-5, Dihydrocapsaicin 19408-84-5D, Dihydrocapsaicin, derivs. 19982-08-2, Memantine 20279-06-5, Homodihydrocapsaicin 20279-06-5D, Homodihydrocapsaicin, derivs. 23210-56-2, Ifenprodil 25775-90-0, Civamide 25775-90-0D, Civamide, derivs. 27203-92-5, Tramadol 28789-35-7, Nordihydrocapsaicin 28789-35-7D, Nordihydrocapsaicin, derivs. 31078-36-1, n-Vanillyldecanamide 31078-36-1D, n-Vanillyldecanamide, derivs. 36282-47-0, Tramadol hydrochloride 56995-20-1, Flupirtine 58493-47-3, n-Vanillyloctanamide 58493-47-3D, n-Vanillyloctanamide, derivs. 58493-48-4, Homocapsaicin 58493-48-4D, Homocapsaicin, derivs. 77086-21-6, Dizocilpine 77086-22-7, MK 801 80456-81-1, O-Desmethyl tramadol 119431-25-3, Eliprodil 132014-88-1, Cppene 147441-56-3, Tramadol N-oxide
(novel pharmaceutical compns. for treating chronic pain and pain associated with neuropathy containing N-methyl-D-aspartate receptor antagonist
in combination with μ-opiate analgesic)

L8 ANSWER 11 OF 14 USPATFULL on STN

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TITLE:	Methods and Compositions		
INVENTOR(S):	Nadeson, Raymond, Lethbridge, AUSTRALIA Tucker, Adam Paul, Hawthorn, AUSTRALIA Goodchild, Colin, Malvern, AUSTRALIA		
PATENT ASSIGNEE(S):	CNSBio Pty Ltd, Melbourne, AUSTRALIA (non-U.S. corporation)		
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LINE COUNT: 2617
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compositions of flupirtine for management of neuropathic or inflammatory pain optionally including one or more other analgesics including opiates, NSAIDS and other active. . .
DRWD . . . carrageenan-induced hyperalgesia in male Wistar rats, where paw flick latency (seconds) is plotted against time (minutes) for saline controls (diamonds), flupirtine at 5 mg/kg (squares), flupirtine at 10 mg/kg (stars), morphine at 0.8 mg/kg (vertical bars), morphine at 1.6 mg/kg (horizontal bars), the combination of flupirtine at 5 mg/kg with morphine at 0.4 mg/kg (squares) and the combination of flupirtine at 10 mg/kg with morphine at 0.4 mg/kg (circles).
DRWD . . . Wistar rats, where standardized ECT value as a ratio against the control is plotted against time for saline controls (triangles), flupirtine at 5 mg/kg (diamonds), morphine at 0.4 mg/kg (circles) and the combination of flupirtine at 5 mg/kg with morphine at 0.4 mg/kg (squares); and
DRWD . . . threshold (grams) is plotted against time (minutes), where zero time is time of test drug injection, for saline controls (diamonds), flupirtine at 5 mg/kg (squares), flupirtine at 10 mg/kg (triangles), morphine at 1.6 mg/kg (crosses), morphine at 3.2 mg/kg (stars), the combination of flupirtine at 5 mg/kg with morphine at 3.2 mg/kg (closed circles) and the combination of flupirtine at 10 mg/kg with morphine at 1.6 mg/kg (open squares), with results for weight matched non-diabetic controls shown with an open circle.
DETD . . . years and frequently cannot be associated with a single injury. Chronic pain predominantly constitutes chronic inflammatory pain (e.g. arthritis) or "neuropathic pain" which can be defined as pain initiated or caused by a primary lesion or dysfunction within the nervous system (Mersky. . . Bogduk Classifications of Chronic Pain, 2.sup.nd edn. Seattle LASP Press: 394, 1994, De Andres and Garcia-Ribas Pain Practice 3:1-7, 2003). Neuropathic pain is associated with a variety of disease states and present in the clinic with a wide range of symptoms. (Woolf. . .
DETD Neuropathic pain is often reported as having a lancinating or continuous burning character and is frequently associated with the appearance of abnormal. . . a painful response, and hyperalgesia is characterized by an increased pain response to normally non-painful stimuli. Some disorders characterized by neuropathic pain include monoradiculopathies, trigeminal neuralgia, postherpetic neuralgia, phantom limb pain, complex regional pain syndromes, back pain and the various peripheral neuropathies. Neuropathic pain may also be associated with diabetes, radio- or chemo-therapy and infections such as HIV. Neuropathic pain may also result as a side effect of drug treatment or abuse.
DETD Neuropathic pain can be characterized by the following clinical features (Teng and Mekhail Pain Practice 3:8-12, 2003, Rajbhandari et al Pain, 83:627-629,. . . has a burning or electrical quality with an occasional paroxysmal, brief, shooting, or stabbing quality.
2. Although the onset of most neuropathic pain is within days after the precipitating injury, there is no absolute temporal relationship to the originating neural trauma such that. . .

DETD . . . available therapies for acute pain caused by stimulation of the nociceptors, especially treatment with opioid and non-steroidal anti-inflammatory drugs (NSAIDs), neuropathic pain is an area of largely unmet therapeutic need. Due to the distinct pathophysiochemical mechanisms and clinical manifestations associated with neuropathic pain relative to pain caused as a result of nociceptor stimulation or acute pain, agents useful in the treatment of pain caused as a result of nociceptor stimulation or acute pain have reduced effectiveness in neuropathic pain treatment. In particular, the effectiveness of opioids in the treatment of neuropathic pain is diminished relative to their use in the treatment of pain caused as a result of nociceptor stimulation or acute pain, and drug dose response curves for treatment of neuropathic pain are shifted to the right of those for treatment of pain caused as a result of nociceptor stimulation or acute. . .

DETD Due to the diminished effects of opioids in subjects suffering from neuropathic pain, the use of opioids is often frequent and sustained. This over use is often associated with addiction, the development of. . .

DETD The conventional pharmacological mainstays of clinical management of neuropathic pain are the tricyclic anti-depressants and certain anti-convulsants, but even these achieve a reduction in pain of less that 50% in. . .

DETD . . . treat, alleviate, prevent, diminish or otherwise ameliorate the symptoms associated with neuropathic and/or inflammatory pain in a subject. Reference to "neuropathic pain" or "inflammatory pain" includes the neuropathic or inflammatory component of nociceptive pain. In particular, the present invention contemplates a method. . . inducing an analgesic response to neuropathic or inflammatory pain in a mammal comprising administering to the mammal an amount of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof effective to reduce the level of or otherwise ameliorate the. . .

DETD . . . response in a mammal suffering neuropathic or inflammatory pain by administering to the mammal one of an analgesic agent or flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof concurrently, separately or sequentially with respect to the other of an analgesic agent or flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof, in an amount effective to reduce the level of or otherwise ameliorate the sensation of pain. Preferably, the flupirtine or a pharmaceutically acceptable salt derivate, homolog or analog thereof is administered in an amount effective to reduce at least. . . Preferably, the analgesic agent is an opioid, such as but not limited to fentanyl, oxycodone, codeine, dihydrocodeine, dihydrocodeinone enol acetate, morphine, desomorphine, apomorphine, diamorphine, pethidine, methadone, dextropropoxyphene, pentazocine, dextromoramide, oxymorphone, hydromorphone, dihydromorphine, noscapine, papverine, papveretum, alfentanil, buprenorphine and tramadol and pharmaceutically. .

DETD Another embodiment the present invention relates to the use of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof in the manufacture of a medicament for inducing an analgesic. . . the treatment of neuropathic or inflammatory pain. Preferably, the analgesia is induced without overt

sedation and preferably the pain is neuropathic pain
.

DETD In a further embodiment, the present invention relates to the use of an analgesic agent and flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof, in the manufacture of one or more separate or combined medicaments for inducing analgesia in response to inflammatory or neuropathic pain. Preferably, the analgesia is induced without overt sedation and preferably the pain is neuropathic pain . In a preferred embodiment the analgesic agent is an opioid and preferably the opioid is selected from one or more. . .

DETD . . . or other pathology wherein the treatment of the disease, condition or pathology is conducted in association with pain management using flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof or optionally an opioid or another analgesic compound.

DETD . . . delivery system for inducing analgesia in response to neuropathic or inflammatory pain in a mammal comprising an analgesic agent and flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof. In a preferred embodiment the analgesic agent is an opioid. . .

DETD . . . pain, inflammation or a neurological condition which has a neuropathic or inflammatory pain component, the treatment comprising the administration of flupirtine and optionally an opioid or a pharmaceutically acceptable salts, derivatives, homologs or analogs thereof.

DETD Preferably, the flupirtine or pharmaceutically acceptable salt, derivative, homolog or analog thereof is administered at a dose of between about 0.5 mg/kg and. . .

DETD A further aspect of the subject invention provides a system for the controlled release of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof and optionally an opioid, alone or together with another analgesic. . .

DETD The present invention further provides an agent for inducing an analgesic response in a mammal, the agent comprising flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof and optionally an analgesic compound such as an opioid and. . . a treatment protocol for cancer, the protocol comprising the administration of a anti-cancer agent and/or radiation therapy in combination with flupirtine and optionally an opioid or a pharmaceutically acceptable salt, derivative, homolog or analog thereof.

DETD . . . "effective amount" and "therapeutically effective amount" of an agent as used herein mean a sufficient amount of the agent (e.g. flupirtine and/or an opioid) to provide the desired therapeutic or physiological effect or outcome. Undesirable effects, e.g. side effects, are sometimes. . .

DETD Throughout this specification, the term "neuropathic pain" is to be understood to mean pain initiated or caused by a primary lesion or dysfunction within the nervous system. Examples of categories of neuropathic pain that may be treated by the methods of the present invention include monoradiculopathies, trigeminal neuralgia, postherpetic neuralgia, phantom limb pain, complex regional pain syndromes, back pain, neuropathic pain associated with AIDS and infection with the human immunodeficiency virus and the various peripheral neuropathies, including, but not limited to. . .

DETD Reference to "neuropathic pain" or inflammatory pain" includes reference to a neuropathic or inflammatory component of nociceptive pain.

DETD . . . 70% and particularly preferably at least 85%. In a most preferred aspect of the present invention, the sensibility to the neuropathic pain is completely, or substantially completely, removed. To assess the level of reduction of sensibility to pain associated with the analgesia. . .

DETD . . . inducing an analgesic response to neuropathic or inflammatory pain in a mammal comprising administering to the subject an amount of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof effective to reduce the level of or otherwise ameliorate the. . .

DETD . . . analgesia in a mammal suffering neuropathic or inflammatory pain by administering to the mammal one of an analgesic agent or flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof concurrently, separately or sequentially with respect to the other of an analgesic agent or flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof, in an amount effective to reduce the level of or. . .

DETD . . . or other pathology wherein the treatment of the disease, condition or pathology is conducted in association with pain management using flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof and optionally in addition to an analgesic agent.

DETD In both cases, the analgesic effect is preferably without overt sedation or the other side effects of flupirtine or the analgesic agent.

DETD Collectively, the flupirtine or pharmaceutically acceptable salt, derivative, homolog or analog thereof and the other analgesic agent will be referred to as the "active agents". A synergistically effective amount of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof, when administered concurrently, separately or sequentially with an analgesic agent. . .

DETD GABAergic drugs can also be used in combination with flupirtine for the treatment of neuropathic and inflammatory pain. GABAergic drugs include compounds that enhance the action of gamma aminobutyric acid. . .

DETD . . . of an opioid receptor. Opioid compounds are well known and include naturally occurring compounds derived from opium such as codeine, morphine and papavarine as well as derivatives of such compounds that generally have structural similarity as well as other structurally unrelated. . . mammalian system. Specific examples of opioid compounds contemplated by the present invention include: fentanyl, oxycodone, codeine, dihydrocodeine, dihydrocodeinone enol acetate, morphine, desomorphine, apomorphine, diamorphine, pethidine, methadone, dextropropoxyphene, pentazocine, dextromoramide, oxymorphone, hydromorphone, dihydromorphine, noscapine, nalbuprhine papaverine, papaveretum, alfentanil, buprenorphine and tramadol and. . .

DETD . . . that the preferred route will vary with the condition and age of the subject, the nature of the inflammatory or neuropathic pain being treated, its location within the subject and the judgement of the physician or veterinarian. It will also be understood. . .

DETD . . . days, weeks or months. Suitable dosage amounts and regimes can be determined by the attending physician or veterinarian. For example, flupirtine or pharmaceutically acceptable salts, derivatives, homologs or analogs thereof, may be administered to a subject at a rate of between. . . accordance with dosing rates in practice. For example, fentanyl can be administered in an amount of about 100 μg whereas morphine may be administered in an amount of 10 mg, also on an hourly basis. The administration amounts may be varied. . .

DETD In relation to combination to therapy, flupirtine or its pharmaceutically acceptable salts, derivatives, homolog or analogs thereof and optionally together with an analgesic agent such as an. . .

DETD In one particular embodiment, flupirtine or its pharmaceutically acceptable salts, derivatives, homologs or analogs thereof and optionally an analgesic agent such as a opioid is. . . Uroplakins, Uterine sarcoma, Uterus Cancer, Vaginal Cancer, Vulva Cancer, Waldenstrom's-Macroglobulinemia or Wilms' Tumor. In some cases, the treatment potential of flupirtine and optionally an opioid and/or anti-cancer agent may also include a pronopshine.

DETD . . . protocol comprising the steps of administering to said subject, an effective amount of an anti-cancer agent and an amount of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof effective to reduce the level of or otherwise ameliorate the. . . include any of those listed above. Administration of the anticancer agent may be sequential or simultaneous or independent of the flupirtine.

DETD . . . protocol comprising the steps of administering to said subject, an effective amount of an anti-inflammatory agent and an amount of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof effective to reduce the level of or otherwise ameliorate the. . . include any of those listed above. Administration of the anti-inflammatory agent may be sequential or simultaneous or independent of the flupirtine.

DETD . . . of administering to said subject, an effective-amount of an agent used to treat a neurological condition and an amount of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof effective to reduce the level of or otherwise ameliorate the. . . above. Administration of an agent used to treat a neurological disease may be sequential or simultaneous or independent of the flupirtine.

DETD . . . pain during the treatment of or amelioration of symptoms of any one or more of the following diseases which cause neuropathic pain or which have a neuropathic pain component: Abdominal Wall Defect, Abdominal Migraine, Achondrogenesis, Achondrogenesis Type IV, Achondrogenesis Type III, Achondroplasia, Achondroplasia Tarda, Achondroplastic Dwarfism, Acquired hnmunodeficiency. . .

DETD . . . comprising the steps of administering to said subject, an effective amount of an a disease condition and an amount of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof effective to reduce the level of or otherwise ameliorate the. . . include any of those listed above. Administration of the disease condition may be sequential or simultaneous or independent of the flupirtine.

DETD The present invention also relates to compositions comprising flupirtine or a pharmaceutically acceptable salt, derivative,

homolog or analog thereof, optionally with another analgesic agent such as an opioid, together. . .

DETD . . . present invention may be packaged for sale with other active agents or alternatively, other active agents may be formulated with flupirtine or its pharmaceutical salts, derivatives, homologs or analogs thereof and optionally an analgesic agent such as an opioid.

DETD Thus, a further particular aspect of the present invention provides a system for the controlled release of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof and optionally an opioid, alone or together with another analgesic. . .

DETD In another embodiment, a multiparticulate release flupirtine composition for oral administration is provided. The formulation is made by complexing flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof optionally together with an opioid and/or other analgesic or active. . .

DETD Still another aspect of the present invention provides a composition comprising: (a) a flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof; (b) an active component having a delayed time of release;. . .

DETD . . . ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacyl morphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide,. . .

DETD Reference to morphine or other opioids includes oral and slow release agents. For example, kapanol is a slow release morphine and ordine is a oral morphine.

DETD . . . improver is water-soluble polyethoxylated caster oil and an example of a suitable surfactant is Cremophor EL. Dose ranges suitable for flupirtine or pharmaceutical salts, derivatives, homologs or analogs thereof are for example 100 to 1500 mg orally, every six hours including 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500. Suitable dose ranges for morphine are 2.5 to 20 mg every 3 to 6 hours such as 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6,. . .

DETD In combination with flupirtine, the dosage intervals are preferably from about 12 to 24 hours.

DETD . . . devices for introduction to or in a body or body cavity coated with a sustained or slow release formulation of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof. Optionally, an opioid alone or with other active agents is. . .

DETD The present invention further provides an implantable medical device having an outer surface covered at least in part by a flupirtine or a pharmaceutically acceptable salts, derivative, homolog or analog and optionally an opioid and/or other active agent, a conformal coating. . .

DETD . . . of the experimental parameters considered in the Examples is the ability to avoid side effects such as sedative effects of morphine or its homology, when used in combination with flupirtine.

DETD Groups of rats were tested with the rotarod as above with the following treatments:

(a) Saline
(b) Morphine at doses of 0.4, 0.8, 1.6, 3.2, and 6.4 mg/kg
(c) Flupirtine at doses of 5, 10 and 20 mg/kg
(d) A combination of flupirtine at 5 mg/kg with morphine at 0.4 mg/kg
(e) A combination of flupirtine at 10 mg/kg with morphine at 1.6 mg/kg

DETD
TABLE 1

Treatment	Lowest run time (s) n	mean	SD
saline control	30	119.2	2.8
flupirtine 5 mg/kg ip alone	18	118.4	6.1
flupirtine 10 mg/kg ip alone	20	107.7	36.7
flupirtine 20 mg/kg ip alone*	10	58.1*	54.5
morphine 0.4 mg/kg ip alone	10	120	0
morphine 0.8 mg/kg ip alone	10	120	0
morphine 1.6 mg/kg ip alone	10	110.4	19
morphine 3.2 mg/kg ip alone	10	99.6	41.7
morphine 6.4 mg/kg ip alone*	10	60*	41.7
flupirtine 5.0 mg/kg + morphine 0.4 mg/kg 1.3 together ip	10	119.5	
flupirtine 10 mg/kg + morphine 1.6 mg/kg 4.45 together ip	10	117	

one way Anova + Tukey-Kramer post-hoc test: compared with saline control
*p < 0.05

DETD It can be concluded from these experiments that sedation is caused by doses of flupirtine greater than 10 mg/kg and morphine greater than 3.2 mg/kg.

DETD The following drug treatments were given to separate groups of rats:

Saline controls
Flupirtine at doses of 5 and 10 mg/kg alone
Morphine at doses of 0.4, 0.8 and 1.6 mg/kg alone
Combinations of flupirtine at 5 and 10 mg/kg with morphine at 0.4 mg/kg

DETD
TABLE 2

Treatment	Pre-treatment mean	SD	n	Post-treatment mean	SD	n
saline controls	10.98	2.27	72	6.22	2.18	72
flupirtine 5 mg/kg ip alone	10.90	2.80	30	5.82	1.70	30
flupirtine 10 mg/kg alone	10.97	2.42	24	5.51	2.13	24
morphine 0.4 mg/kg ip alone	12.10	2.30	36	5.76	3.10	36
morphine 0.8 mg/kg alone	10.02	1.75	27	4.88	1.67	27
morphine 1.6 mg/kg alone	10.30	2.48	72	8.88	3.15	72

flupirtine 5 mg/kg and morphine 11.60 2.25 72 8.75
3.31 72
0.4 mg/kg ip together
flupirtine 10 mg/kg and morphine 9.66 1.46 54 10.34
4.02 54
0.4 mg/kg ip together
DETD Flupirtine 5 and 10 mg/kg or morphine 0.4 and 0.8 mg/kg alone had no effect on carrageenan-induced hyperalgesia. The combination of flupirtine 5 mg/kg with morphine 0.4 mg/kg caused significant reversal of carrageenan-induced hyperalgesia and this was equal to the effect of 1.6 mg/kg morphine given alone; flupirtine increased the antinociceptive effect of morphine fourfold. Flupirtine 5 mg/kg in combination with morphine 0.4 mg/kg led to significantly less hyperalgesia compared with saline or either drug alone *p<0.001 one way ANOVA with Tukey-Kramer post hoc test. Finally, complete reversal of carrageenan-induced hyperalgesia was caused by 10 mg/kg flupirtine in combination with 0.4 mg/kg morphine i.e., doses of two drugs that were ineffective when given alone caused complete antinociception in this model of neuropathic pain (p>0.05 in comparison with pre carrageenan levels (at -20, -10 and 0 mins in graph above)--one way ANOVA with Tukey-Kramer. . . .
DETD . . . and plotted as time response curves shown in FIG. 2 for groups of rats that received the following treatments:

Flupirtine at a dose of 5 mg/kg ip alone
Flupirtine at a dose of 10 mg/kg ip alone
Morphine at a dose of 0.4 mg/kg ip alone
A combination of morphine at a dose of 0.4 mg/kg with flupirtine at a dose of 5 mg/kg
DETD . . . 3

SUMMARY DATA ECT PARADIGM		n rats	n observations	mean	SD
saline controls	per	16	48	1.00	0.05
	post		90	1.27	0.35
flupirtine 5 mg/kg	pre	20	60	1.00	0.05
	post		100	1.54	0.64
flupirtine 10 mg/kg	pre	4	12	1.00	0.07
	post		20	1.92	0.79
morphine 0.4 mg/kg	pre	12	36	1.00	0.06
	post		60	1.46	0.53
combination morphine 0.4 mg/kg and flupirtine 5 mg/kg	pre	12	36	1.00	0.09
	post		60	1.91	0.89

DETD . . . one way ANOVA with Tukey-Kramer post hoc test was applied to the data in the table above. ECT values after flupirtine 5 or 10 mg/kg, morphine 0.4 mg/kg or the combination of morphine 0.4 mg/kg with flupirtine 5 mg/kg were all significantly greater than saline (p<0.001). There was significant antinociception following flupirtine alone at 5 or 10 mg/kg and morphine 0.4 mg/kg (p<0.001). The amount of antinociception following morphine 0.4 mg/kg/ flupirtine 5 mg/kg combination was significantly greater than

morphine 0.4 mg/kg or flupirtine 5 mg/kg given alone ($p<0.001$). It is therefore concluded that non-sedative doses of flupirtine can increase the antinociception following morphine without causing sedation.

DETD The treatment of neuropathic pain states, including diabetic neuropathy in humans is frequently unsatisfactory. Current pharmacological regimens consist of the tricyclic antidepressants (Sindrup et al.,. . . Suppl. 9 S17-S25, 1995; Avidan et al., Israel Journal of Medical Sciences, 32:331-334, 1996). It is accepted generally that human neuropathic pain states are resistant to opioid treatment (Arner et al. supra). Some researchers have found that opioids may produce antinociceptive effects in neuropathic pain models but at higher than normal doses that also cause sedation revealed by tests such as open field activity monitoring. . .

DETD Courteix and co-workers have developed a diabetes-induced model for neuropathic pain. They found that induction of experimental insulin-dependent diabetes mellitus in rats caused allodynia and hyperalgesia (Courteix et al., Pain, 53:81-88, 1993). They went on to show that intravenous morphine induced a dose-dependent antinociceptive effect at doses twice as high as those in normal rats, using the mechanical nociceptive paw pressure test (Courteix et al., Pain, 53 supra). Thus the diabetic model reproduced the experience of diabetic neuropathic pain in humans; it is opioid resistant. The experiments reported here use this model to assess the relative efficacy of flupirtine and morphine given alone and in combinations in causing antinociception assessed with paw pressure measured using the Randall Sellito method.

DETD . . . pressure nociceptive thresholds below 30 g (60% of the value in normal weight matched rats) were deemed to have developed hyperalgesia/ neuropathic pain and thus used in further experiments.

DETD . . . also at 20, 30 and 40 minutes after intraperitoneal (ip) injections of:

saline (controls)
weight matched non diabetic controls (no treatment)
flupirtine 5 mg/kg alone
flupirtine 10 mg/kg alone
morphine 1.6 mg/kg alone
morphine 3.2 mg/kg alone
flupirtine 5 mg/kg plus morphine 3.2 mg/kg together
flupirtine 10 mg/kg plus morphine 1.6 mg/kg together

DETD . . . diabetic controls n = 21 rats 63 44.7 6.9
saline controls n = 16 rats 48 28.54 4.12
48 30.94 5.89
flupirtine 5 mg/kg alone n = 21 rats 63
28.25 4.50 63 31.90 7.15
flupirtine 10 mg/kg alone n = 15 rats 45
27.89 5.69 45 41.00 14.56
morphine 1.6 mg/kg alone n = 14 rats 42
28.10 5.84 42 31.90 6.98
morphine 3.2 mg/kg alone n = 8 rats 24
26.67 4.82 24 35.00 10.11
flupirtine 5 mg/kg + morphine 3.2 mg/kg together n = 8
24 26.67 4.08 24 36.88 12.84
rats

flupirtine 10 mg/kg + morphine 1.6 mg/kg together n = 17
51 28.82 5.16 51 49.41 15.55
rats
DETD Complete reversal of streptozotocin-induced diabetic hyperalgesia was caused by flupirtine 10 mg/kg given alone and also flupirtine 10 mg/kg+morphine 1.6 mg/kg together ($p>0.05$); i.e., the paw withdrawal thresholds after the drug treatment were not statistically different from thresholds for normal non-diabetic weight matched controls. Flupirtine 5 mg/kg alone and morphine 1.6 mg/kg alone cause no significant reversal of diabetes-induced hyperalgesia; the paw withdrawal thresholds after the drug injection were not significantly different compared with the thresholds in those rats measured before the drug was injected ($p>0.05$). Morphine 3.2 mg/kg given alone caused significant antinociception; paw thresholds did increase significantly after the drug ($p<0.05$) but those values and the size of that response were significantly less than that caused by a lower dose of morphine (1.6 mg/kg shown to be ineffective when it was given alone) given in combination with flupirtine 10 mg/kg ($p<0.001$). Finally, flupirtine 10 mg/kg in combination with morphine 1.6 mg/kg caused greater antinociception than flupirtine 10 mg/kg alone.
DETD The results reported in Examples 2 through 4 show that non-sedative doses of flupirtine increases the overall antinociceptive effect of morphine without causing sedation in three animal models of pain; electrical, inflammatory and neuropathic. In neuropathic and inflammatory pain models it is possible, using flupirtine in combination with morphine, to cause such significant antinociception as to reverse hyperalgesia such that animals with these pain states are rendered normal with respect to pain sensitivity. This demonstrates utility of flupirtine as an adjunct to opioid analgesics especially in pain states such as inflammatory and neuropathic pain, which are either opioid resistant to the extent that only partial analgesia can be achieved with opioid drugs or are at doses that cause side effects such as sedation. The co-administration of flupirtine with the opioid offers improved pain control in inflammatory and neuropathic pain with doses and combinations that are not accompanied by sedation.
DETD Clinical Applications of Flupirtine
DETD . . . establish outcomes and variables that might be most useful to evaluate in larger double blind studies
Show that the administration of flupirtine to cancer patients with neuropathic pain can improve pain experience
Define the dose
Quantify the pain reduction along with reduction in the use of other analgesics, including morphine
Estimate the impact on quality of life
Show an improvement in side effects and complications of analgesic drug treatments
DETD . . . approval and written informed consent from each patient were obtained. All patients referred to the palliative care unit with cancer-related neuropathic pain were considered eligible for entry if they had been receiving opioids for at least 48 hours. The trial lasted eight. . . . experiences as well as drug usage. On day 1 there was 24 hours observation and baseline measurements before

commencement on flupirtine at a dose of 100 mg four times daily (qid). If the pain was not controlled and there was no. . . clinical need. Patients were encouraged to take their normal opioid and co-analgesics concurrently including any "breakthrough" doses of immediate release morphine mixture.

DETD . . . of the disease into his pelvis and developed liver and pelvic metastases in early 2003. JE had been experiencing intermittent neuropathic pain in his left thigh and buttock for the last two years prior to presentation for a trial of flupirtine . This had been increasing in the two weeks prior to his admission. He described his pain as "a blow torch. . . thigh. JE subsequently received radiotherapy to this area, and this only provided temporary relief. JE had been prescribed sustained release morphine (Kapanol) 50 mg mane and 100 mg nocte with immediate release morphine mixture (Ordine) 80 mg as required for breakthrough pain. This regimen has been unsuccessful in managing his pain. JE was. . .

DETD Summary of Events During Flupirtine Trial (See Accompanying Table)

DETD . . . Kapanol and 260 mg Ordine together with dexamethasone 4 mg daily plus Epilim 600 mg and Endep 25 mg. His neuropathic pain discriminant function score: was 0.862. This is a function calculated from measurements of twelve different symptoms widely accepted to be indicative of neuropathic pain; a score >0 indicates that the pain is neuropathic (Krause and Backonja. The Clinical Journal of Pain 19: 306-314 2003).. . .

DETD Day 1: In the 24 hours before commencement on flupirtine JE's opioid usage was 100 mg Kapanol and 310 mg Ordine plus adjuncts: dexamethasone 4 mg; Epilim 600 mg; Endep 25 mg. Neuropathic pain discriminant score: was 2.448, average pain score: 8/10, least pain: 1/10 and worst pain: 10/10. WHO performance status was scored. . .

DETD Day 2: JE had been taking flupirtine 100 mg QID for 24 hours. Opioid usage for last 24 hours was 150 mg Kapanol with adjuncts: dexamethasone 4 mg; Epilim 600 mg; Endep 25 mg and paracetamol 1 g. His discriminant neuropathic pain score had fallen to a non-neuropathic level: -1.238. The average pain score was 2/10, least pain: 0/10, worst pain: 3/10. . .

DETD Day 3: JE continued taking flupirtine 100 mg QID. Opioid usage for last 24 hours: 150 mg Kapanol plus adjuncts: dexamethasone 4 mg daily, Epilim 600 mg daily and Endep 25 mg. His neuropathic pain discriminant score had fallen to the minimum level indicating no pain at all: -1.408. His average pain score: 0/10; least. . . He reported that he was feeling "very well", his appetite had increased and he had no pain at all. The flupirtine dose for the next 24 hours was increased to 200 mg QID and Kapanol reduced by 30 mg/24 hours.

DETD Day 4: JE was taking flupirtine 200 mg QID. Opioid usage for last 24 hours: 120 mg Kapanol with adjuncts: dexamethasone 4 mg daily; Epilim 600 mg daily; Endep 25 mg. His neuropathic pain discriminant score remained at the minimum score of -1.408. Average pain score: 0/10; least pain: 0/10; worst pain: 0/10 and. . . colostomy was also yet to function (2). However, he had not experienced any fullness and his appetite remained good. The flupirtine dose was reduced to 100 mg QID and the Kapanol to 80 mg/24 hours.

DETD Day 5: JE continued to take flupirtine 100 mg QID. Opioid

usage for last 24 hours: 80 mg Kapanol and adjuncts: dexamethasone 4 mg daily; Epilim 600 mg daily and Endep 25 mg. The neuropathic pain discriminant score remained at the minimum score of -1.408. The average pain score: 0/10; least pain: 0/10; worst pain: 6/10. . .

DETD Day 6: The flupirtine dose remained at 100 mg QID. Opioid usage for last 24 hours: 40 mg Kapanol and adjuncts: dexamethasone 2 mg plus Endep 25 mg only. His neuropathic pain discriminant score: -1.048, average pain score: 8/10, least pain: 0/10, worst pain: 9/10 and WHO performance status: 3. JE was. . .

DETD Day 7: JE continued to take flupirtine at the dose of 100 mg QID. Opioid usage for last 24 hours: 40 mg Kapanol with adjuncts: dexamethasone 2 mg and Endep 25 mg. His neuropathic pain discriminant score had returned to the minimum score of -1.408. His average pain score: 0/10; least pain: 0/10; worst pain:. . . drowsiness (3) and the myoclonic twitch (2). However, he was able to concentrate for longer periods and remained free from neuropathic pain symptoms. His appetite remained poor (3). However, his colostomy was functioning regularly. JE had also complained of spider hallucinations (2),. . . worried by them, as he was aware that they were not really there. He had a similar experience while on morphine in the past. The Endep and Kapanol were ceased and Oxycontin 20 mg BD commenced to address this problem.

DETD Day 8: JE continued to take flupirtine 100 mg QID. Opioid usage for the previous 24 hours: 40 mg Oxycontin (sustained release oxycodone)+5 mg Endone (immediate release oxycodone). Oxycodone is approximately twice as potent as morphine and thus JE was taking opioid at a dose equivalent to 90 mg morphine. He also took dexamethasone 2 mg. The neuropathic pain discriminant score was 0.677 with average pain score for the previous 24 hours: 7/10; least pain: 0/10; worst pain: 9/10. . .

DETD Summary of Events after Flupirtine Trial

DETD On the following day JE was discharged home taking flupirtine dose 100 mg QID with Oxycontin 40 mg/24 hrs. His average pain score for the previous 24 hours was 0/10,. . .

DETD Day 18: JE at home, taking flupirtine dose 100 mg QID, Oxycontin 20 mg BD. endone 5 mg for breakthrough required 2-3 during the week and dexamethasone 4 mg for a low platelet count. He had no neuropathic pain symptoms. He said that he was "feeling well, eating everything and getting out and about. JE was still active at the last follow up on day 44 with no neuropathic pain symptoms taking Oxycontin 20 mg bd with no breakthroughs and leading an active life.

DETD . . . and route of each of the opioids the patient has received over the last 24 hours is translated to parenteral morphine equivalent using a standard conversion table (See Table 5). The total MEDD in mgs is measured each day after assessing. . .

DETD . . . Methadone O 4

Codeine	SC	0.1	Methadone	PO	4
Meperidine	IM	0.1	Methadone	R	4
Meperidine	IV	0.1	Methadone	SC	8
Meperidine	O	0.05	Morphine	EP	1
Meperidine	PO	0.05	Morphine	IM	1
Meperidine	SC	0.1	Morphine	IV	1

Diamorphine PO 0.65 Morphine O
0.4
Diamorphine SC 1.3 Morphine PO
0.4
Fentanyl PO 0.05 Morphine R
0.4
Fentanyl SL 0.05 Morphine SC
1
Fentanyl IV 0.1 Oxycodone PO 0.833
Fentanyl SC 0.1 Oxycodone SC 1.5
Fentanyl TD 0.1 Propoxyphene IM 0.167
Hydromophone IM 5 Propoxyphene. . .
DETD . . . DAY OF OBSERVATION
OBSERVATIONS DAY 0 DAY 1 DAY 2 DAY 3
DAY 4 DAY 5 DAY 6 DAY 7 DAY 8

flupirtine dose in last 24 hours 0 mg 0 mg 100 mg
100 mg 200 mg 100 mg 100 mg 100. . . Kapanol-
150 mg 100 mg 150 mg 150 mg 120 mg 80 mg 40
mg 40 mg 0 mg
sustained release morphine
dose in last 24 hrs: morphine 260 mg 310 mg 0 mg 0
mg 0 mg 0 mg 0 mg 0 mg 0 mg
mixture
dose in last. . . hours: oxycodone 0 mg 0 mg 0 mg 0 mg
0 mg 0 mg 0 mg 0 mg 5 mg
parental morphine equivalent 164 mg 164 mg 60 mg 60
mg 48 mg 32 mg 16 mg 16 mg 37 mg*
dose of. . .
DETD . . . for breakthrough pain. RM was treated with ketaminefor six days prior to this trial; it was ceased 24 hours before flupirtine dosing began. The ketamine failed to control pain and neuropathic pain scores increased towards the end of that treatment (see table below comparing day 0 with day 1. In an attempt. . . the pain RM was also commenced on a cox-2 inhibitor (Celebrex) and an anticonvulsant (Gabapentin) in the weeks before the flupirtine trial began. This regimen had also been unsuccessful in managing his pain.
DETD Summary of Events During Flupirtine Trial
DETD . . . 100 mg daily, Celebrex 400 mg and strict 6 hourly Paracetamol. In spite of this treatment he still had significant neuropathic pain; his neuropathic pain discriminant function score: was 0.077. This is a function calculated from measurements of twelve different symptoms widely accepted to be indicative of neuropathic pain; a score >0 indicates that the pain is neuropathic (Development of a Neuropathic Pain Questionnaire. Krause and Backonja, The Clinical Journal of Pain 19: 306-314, 2003). His average pain score: 5/10, least pain: 0/10. . .
DETD Day 1: In the 24 hours before commencement on flupirtine RM's opioid usage was: 40 mg oxycodone orally, 15 mg Endone orally and 0.5 mg hydromorphone subcutaneously plus adjuncts: Gabapentin. . . hourly Paracetamol. RM was receiving ketamine prior to his transfer, a period of 20.sup.+ hours elapsed before his commencement on flupirtine . Neuropathic pain discriminant score was highly significant at the value of 0.262. His average pain score: 8/10, least

pain: 0/10 and worst. . .

DETD Day 2: RM had been taking flupirtine 100 mg QID for 24 hours. Opioid usage for last 24 hours: 40 mg oxycodone orally and 2.5 mg hydromorphone subcutaneously with adjuncts: Gabapentin 100 mg daily, Celebrex 400 mg and strict 6 hourly Paracetamol. Neuropathic pain discriminant score had fallen dramatically to a non-neuropathic level: -0.228. The average pain score had also fallen to 5/10, least. . .

DETD Day 3: RM continued taking flupirtine 100 mg QID. Opioid usage for last 24 hours: 40 mg oxycodone orally and 2 mg hydromorphone subcutaneously plus adjuncts: Gabapentin 100 mg daily, Celebrex 400 mg and strict 6 hourly Paracetamol. Neuropathic pain discriminant score remained at a low non-neuropathic level: -1.008. His average pain score: 8/10; least pain: 0/10; worst pain: 8/10;. . .

DETD Day 4: RM continued to take flupirtine 100 mg QID. Opioid usage for last 24 hours: 40 mg oxycodone and 5 mg Endone both orally, no hydromorphone breakthrough injections, with adjuncts: Gabapentin 100 mg daily, Celebrex 400 mg and strict 6 hourly Paracetamol. Neuropathic pain discriminant score remaine low and at a non-neuropathic level: -1.138. Average pain score: 8/10; least pain: 0/10; worst pain: 8/10. . . pain relief had been achieved. This compared markedly with the 10% relief he reported on day 1 before treatment with flupirtine.

DETD Day 5: RM continued to take flupirtine 100 mg QID. Opioid usage for last 24 hours: 40 mg oxycodone orally and 1 mg hydromorphone subcutaneously with adjuncts: Gabapentin 100 mg daily, Celebrex 400 mg and strict 6 hourly Paracetamol. Neuropathic pain discriminant score: -1.003. The average pain score: 8/10; least pain: 2/10; worst pain: 9/10 and WHO performance status: 3. RM. . .

DETD Day 6: RM continued taking flupirtine 100 mg QID. Opioid usage for last 24 hours: 40 mg oxycodone orally and 3 mg hydromorphone subcutaneously with adjuncts: Gabapentin 100 mg daily, Celebrex 400 mg and strict 6 hourly Paracetamol. Neuropathic pain discriminant score remained low and non-neuropathic: -1.168. This indicated that the pain being experienced was not of neuropathic origin. The. . . WHO performance status: 3. The neuropathic element to RM's pain appeared to have improved from the first day of taking flupirtine. However he was still experiencing a significant amount of incident pain. Since the reason for addition of flupirtine was to treat the opioid resistant neuropathic pain, the dosage was kept the same but opioid dose was increased, to 30 mg oxycodone orally BD. This follows the concept of this invention of using a combination of opioid with flupirtine in the management of pain states that involve a significant neuropathic pain element that is resistant to the opioid given on its own. He still had some loss of appetite (2), constipation. . .

DETD Day 7: RM continued to take flupirtine 100 mg QID. Opioid usage for last 24 hours: 60 mg oxycodone and 10 mg Endone both orally with adjuncts: Gabapentin 100 mg daily, Celebrex 400 mg and strict 6 hourly Paracetamol. Neuropathic pain discriminant score remained low and non-neuropathic: -1.168. The other pain-scores had all fallen: average pain score 3/10; least pain 0/10;. . .

DETD Day 8: RM continued to take flupirtine 100 mg QID. Opioid usage for last 24 hours: 60 mg oxycodone, 5 mg Endone both orally and 2 mg hydromorphone subcutaneously with adjuncts: Gabapentin 100 mg daily,

Celebrex 400 mg and strict 6 hourly Paracetamol. Neuropathic pain discriminant score: -1.198. The average pain score: 4/10; least pain: 1/10; worst pain: 7/10 and WHO performance status: 3. RM. . . (2) had been poor at times. He was constipated (3) and had received his regular aperients. RM felt that the flupirtine had "been good" even though his pain is still present and wished to remain on his current dose after discharge. . .

DETD . . . DAY OF OBSERVATION

OBSERVATIONS DAY 0 DAY 1 DAY 2 DAY 3 DAY 4 DAY 5 DAY 6 DAY 7 DAY 8

flupirtine dose in last 24 hours 0 mg 0 mg 100 mg 100 mg 100 mg 100 mg 100 mg 100. . . hours: hydromorphone 1.5 mg 0.5 mg 2.5 mg 2 mg 0 mg 1 mg 3 mg 0 mg 2 mg

parenteral morphine equivalent 40.82 48.315 45.82 43.32 37.485 38.32 48.32 58.31 64.145

dose of all opioids added up

dose in last 24 hrs: Celebrex. . .

DETD . . . 1, 2, 3. Wherein animals that were injected with either 3+10.sup.3 or 3+10.sup.4 syngeneic MRMT-1 cells who were treated with flupirtine and morphine showed, when compared to either control animals or animals treated with saline.

DETD Central pain models are used to test the analgesic effects of flupirtine both with and without morphine. The majority of central pain models are based on spinal cord injury (SCI). Dysesthesia is one of the major life-style. . .

DETD . . . to such surgery typically self attack and mutilate the denervated limb. The mice are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine ; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold. . .

DETD . . . last for the entire duration of the study (over 2 months). The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold. . .

DETD . . . the injury side. The evoked pain can develop into bilateral patterns. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine ; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold. . .

DETD . . . lifting of ipsilateral hind paw), autotomy is absent in the SNL. The mice are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold. . .

DETD . . . to L5 ligation and exhibit long lasting hyperalgesia and mechanical allodynia. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine ; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold. . .

DETD . . . induces autotomy and touch allodynia which lasts 15 to 21 days. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for

pain, such as the paw withdrawal threshold. . .
DETD . . . develop within a day after injury, and can last for weeks. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold. . .
DETD . . . nerve. In this model allodynia is seen hours after the injection. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine ; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold. . .
DETD . . . or Taxols or other chemotherapeutic agents also capable of inducing neuropathy. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine ; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold. . .
DETD . . . drug-free days+5 more drug days) resulting in the production of hyperalgesia. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine ; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold. . .
DETD . . . vincristine infusion so as to induce in a dose-dependent tactile allodynia. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine ; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold. . .
DETD . . . by dysesthesia (e.g. numbness, tingling and burning pain) of the hands and feet. Rats are injected with Taxol resulting in neuropathic pain. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold. . .
DETD . . . daily injections (i.p.) of cisplatin which produces mechanical allodynia and hyperalgesia. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold. . .
DETD . . . the nerve. Signs of spontaneous pain (paw lifting) are also visible. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine ; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold. . .
DETD . . . markers occur within 14 days, and can be attenuated by osteoprotegerin. The mice are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine ; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold. . .
DETD . . . 6 days after implantation and last for at least 16 days. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold. . .
DETD . . . cell number)-dependent, and occur within 10-12 days of tumor cell injection. The rats are then divided into three groups: 1)

flupirtine alone; 2) flupirtine and morphine ; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold. . .

CLM What is claimed is:
43. A method for inducing an analgesic response to neuropathic pain in a mammal, said method comprising administering to the mammal, a composition comprising the structure ##STR1## or a pharmaceutically acceptable. . . salt thereof in combination with an opioid selected from the list consisting of fentanyl, oxycodone, codeine, dihydrocodeine, dihydrocodeinone enol acetate, morphine , desomorphine, apomorphine, diamorphine, pethidine, methadone, dextropropoxyphene, pentazocine, dextromoramide, oxymorphone, hydromorphone, dihydromorphine, noscapine, papverine, papveretum, alfentanil, buprenorphine and pharmaceutically acceptable derivates,. . .

CLM What is claimed is:
44. The method of claim 43 further comprising the administration of the opioid concurrently or sequentially to the flupirtine.

CLM What is claimed is:
45. The method of claim 44 wherein the opioid is morphine, fentanyl, oxycodone or a pharmaceutically acceptable salt thereof.

CLM What is claimed is:
. . . of any one of claims 43 to 45 wherein the opioid does not induce overt sedation in the presence of flupirtine.

CLM What is claimed is:
47. The method of claim 43 wherein flupirtine is administered in an amount of about 0.5 mg/kg to about 20 mg/kg of body weight.

ST flupirtine pain neuropathic inflammatory
IT Drug delivery systems
(controlled-release; flupirtine compns. for treatment of neuropathic or inflammatory pain treatment)
IT Alzheimer's disease
IT Analgesics
IT Anti-Alzheimer's agents
IT Antiparkinsonian agents
IT Antitumor agents
IT Arthritis
IT Binders
IT Cardiovascular agents
IT Diuretics
IT Human
IT Inflammation
IT Muscle relaxants
IT Neoplasm
IT Pain
IT Parkinson's disease
IT Plasticizers
(flupirtine compns. for treatment of neuropathic or inflammatory pain treatment)
IT Hormones, animal, biological studies
IT Opioids
(flupirtine compns. for treatment of neuropathic or

inflammatory pain treatment)
IT Drug delivery systems
(immediate release; flupirtine compns. for treatment of neuropathic or inflammatory pain treatment)
IT P-glycoproteins
(inhibitors; flupirtine compns. for treatment of neuropathic or inflammatory pain treatment)
IT Nerve, disease
(neuropathy; flupirtine compns. for treatment of neuropathic or inflammatory pain treatment)
IT Anti-inflammatory agents
(nonsteroidal; flupirtine compns. for treatment of neuropathic or inflammatory pain treatment)
IT Alkaloids, biological studies
(opium, hydrochlorides; flupirtine compns. for treatment of neuropathic or inflammatory pain treatment)
IT 57-27-2, Morphine, biological studies 56995-20-1, Flupirtine
(flupirtine compns. for treatment of neuropathic or inflammatory pain treatment)
IT 50-49-7, Imipramine 50-53-3, biological studies 50-55-5, Reserpine 50-78-2, Aspirin 53-86-1, Indomethacin 55-63-0, Nitroglycerin 57-42-1, Pethidine 58-00-4, Apomorphine 58-55-9, Theophylline, biological studies 58-74-2, Papaverine 59-92-7, Levodopa, biological studies 59-96-1, Phenoxybenzamine 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 99-66-1 125-28-0, Dihydrocodeine 128-62-1, Noscapine 299-28-5, Calcium gluconate 357-56-2, Dextromoramide 359-83-1, Pentazocine 427-00-9, Desomorphine 437-38-7, Fentanyl 439-14-5, Diazepam 466-90-0, Dihydrocodeinone enol acetate 466-99-9, Hydromorphone 469-62-5, Dextropropoxyphene 509-60-4, Dihydromorphine 525-66-6, Propranolol 555-30-6, Methyl-dopa 561-27-3, Diamorphine 1617-90-9, Vincamine 4205-90-7, Clonidine 5905-52-2, Ferrous lactate 9004-65-3, Hydroxypropyl methyl cellulose 13655-52-2, Alprenolol 15307-86-5, Diclofenac 22204-53-1, Naproxen 26839-75-8, Timolol 27203-92-5, Tramadol 29122-68-7, Atenolol 29679-58-1, Fenoprofen 31842-01-0, Indoprofen 38194-50-2, Sulindac 51481-61-9, Cimetidine 52485-79-7, Buprenorphine 71195-58-9, Alfentanil
(flupirtine compns. for treatment of neuropathic or inflammatory pain treatment)

L8 ANSWER 12 OF 14 CA COPYRIGHT 2010 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 145:505331 CA
TITLE: Substituted indole compounds having NOS inhibitory activity and their preparation and pharmaceutical composition
INVENTOR(S): Maddaford, Shawn; Ramnauth, Jailall; Rakhit, Suman; Patman, Joanne; Renton, Paul; Annedi, Subhash C.
PATENT ASSIGNEE(S): Neuraxon, Inc., Can.
SOURCE: U.S. Pat. Appl. Publ., 129 pp.
CODEN: USXXCO
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US 20060258721	A1	20061116	US 2006-404267	20060413
US 7375219	B2	20080520		
AU 2006321284	A1	20070607	AU 2006-321284	20060413
CA 2605073	A1	20070607	CA 2006-2605073	20060413
WO 2007063418	A2	20070607	WO 2006-IB3873	20060413
WO 2007063418	A3	20071221		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
EP 1883451	A2	20080206	EP 2006-831851	20060413
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU				
JP 2008535908	T	20080904	JP 2008-505999	20060413
ZA 2007009038	A	20090128	ZA 2007-9038	20060413
BR 2006007517	A2	20090908	BR 2006-7517	20060413
NZ 563191	A	20091127	NZ 2006-563191	20060413
MX 2007012818	A	20080114	MX 2007-12818	20071015
NO 2007005632	A	20080111	NO 2007-5632	20071106
KR 2008021596	A	20080307	KR 2007-726397	20071113
IN 2007CN05128	A	20080627	IN 2007-CN5128	20071113
CN 101247853	A	20080820	CN 2006-80020788	20071211
US 20080249302	A1	20081009	US 2008-47963	20080313
PRIORITY APPLN. INFO.:			US 2005-670856P P	20050413
			US 2006-404267 A1	20060413
			WO 2006-IB3873 W	20060413

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 145:505331
OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

AB . . . stroke, reperfusion injury, neurodegeneration, head trauma, CABG, migraine headache with and without aura, migraine with allodynia, central post-stroke pain (CPSP), neuropathic pain, morphine/opioid induced tolerance and hyperalgesia. Compds. of formula I wherein R1 is H, (un)substituted C1-6 alkyl, (un)substituted C1-4 alkylaryl, and (un)substituted. . .

IT Pain
(neuropathic pain, treatment of; preparation of substituted indole compds. with NOS inhibitory activity useful as therapeutic agents)

IT 57-27-2, Morphine, biological studies 57-42-1, Meperidine 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 77-07-6, Levorphanol 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 125-58-6, Levomethadone 302-41-0, Piritramide 357-56-2, Dextromoramide 359-83-1, Pentazocine 437-38-7, Fentanyl 465-65-6,

Naloxone 466-99-9, Hydromorphone 469-79-4, Ketobemidone 915-30-0, Diphenoxylate 14521-96-1, Etorphine 20290-10-2, Morphine -6-glucuronide 20594-83-6, Nalbuphine 27203-92-5, Tramadol 42408-82-2, Butorphanol 51931-66-9, Tilidine 52485-79-7, Buprenorphine 53179-11-6, Loperamide 53648-55-8, Dezocine 54340-58-8, Meptazinol 56030-54-7 71195-58-9, Alfentanil 132875-61-7, Remifentanil
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of substituted indole compds. with NOS inhibitory activity useful as therapeutic agents)

IT 50-24-8, Prednisolone 50-33-9, Phenylbutazone, biological studies 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-78-2, Aspirin 51-12-7, Nialamide 51-71-8, Phenelzine 52-52-8, 1-Aminocyclopentane-carboxylic acid 53-06-5, Cortisone 53-86-1, Indomethacin 54-92-2, Iproniazid 56-40-6, Glycine, biological studies 58-25-3, Chlordiazepoxide 59-63-2, Isocarboxazid 61-68-7, Mefenamic acid 62-44-2 65-45-2, Salicylamide 68-89-3, Metamizol 72-69-5, Nortriptyline 83-98-7, Orphenadrine 99-66-1 108-01-0, Deanol 113-53-1, Dothiepin 125-71-3, Dextromethorphan 129-20-4, Oxyphenbutazone 155-09-9, Tranylcypromine 298-46-4, Carbamazepine 303-49-1, Clomipramine 315-72-0, Opipramol 438-60-8, Protriptyline 469-62-5, Dextropropoxyphen 479-92-5, Propyphenazone 530-78-9, Flufenamic acid 555-57-7, Pargyline 630-93-3, Phenyloin 644-62-2, Meclofenamic acid 655-05-0, Thozalinone 726-99-8 739-71-9, Trimipramine 768-94-5, Amantadine 853-34-9, Kebuzone 938-73-8, Ethenzamide 1668-19-5, Doxepin 1977-11-3, Perlapine 2210-63-1, Mofebutazone 3286-46-2, Sulbutiamine 3362-45-6, Noxiptilin 4394-00-7, Niflumic acid 4498-32-2, Dibenzepin 4757-55-5, Dimetacrine 5104-49-4, Flurbiprofen 5118-29-6, Melitracen 5560-72-5, Iprindole 5653-80-5 6740-88-1, Ketamine 6829-98-7, Imipramine-N-oxide 7439-93-2, Lithium, biological studies 10262-69-8, Maprotiline 10321-12-7, Propizepine 13669-70-0, Nefopam 14028-44-5, Amoxapine 15301-93-6, Tofenacin 15307-86-5, Diclofenac 15574-96-6, Pizotyline 15676-16-1, Sulpiride 15687-27-1, Ibuprofen 17780-72-2, Clorgyline 18464-39-6, Caroxazone 19794-93-5, Trazodone 19982-08-2, Memantine 21730-16-5, Metapramine 22071-15-4, Ketoprofen 22204-53-1, Naproxen 22345-47-7, Tofisopam 22494-42-4, Diflunisal 23047-25-8, Lofepramine 23651-95-8, Droxidopa 24219-97-4, Mianserin 24526-64-5, Nomifensine 24701-51-7, Demexiptiline 25451-15-4, Felbamate 25905-77-5, Minaprine 26171-23-3, Tolmetin 26629-87-8, Oxaflozane 28721-07-5, Oxcarbazepine 29218-27-7, Toloxatone 29679-58-1, Fenoprofen 29975-16-4, Estazolam 30223-48-4 30544-47-9, Etofenamate 31721-17-2, Quinupramine 32359-34-5, Medifoxamine 33005-95-7, Tiaprofenic acid 34552-84-6, Isoxicam 34911-55-2, Bupropion 35764-73-9, Fluotracen 35941-65-2, Butriptyline 36322-90-4, Piroxicam 37115-32-5, Adinazolam 38194-50-2, Sulindac 40828-46-4, Suprofen 41717-30-0, Befuraline 42924-53-8, Nabumetone 46817-91-8, Viloxazine 52463-83-9, Pinazepam 52942-31-1, Etoperidone 53164-05-9, Acemetacin 53808-88-1, Lonazolac 54188-38-4 54403-19-9 54739-18-3, Fluvoxamine 54739-19-4, Clovoxamine 54910-89-3, Fluoxetine 56775-88-3, Zimelidine 56995-20-1, Flupirtine 57262-94-9, Setiptiline 57574-09-1, Amineptine 57982-78-2, Budipine 59729-33-8, Citalopram 59804-37-4, Tenoxicam 59859-58-4, Femoxetine 60142-96-3, Gabapentin 60662-16-0 60719-82-6, Alaproclate 60929-23-9, Indeloxazine 61413-54-5, Rolipram 61869-08-7, Paroxetine 62305-86-6 62473-79-4, Teniloxazine 63638-91-5, Brofaromine 63758-79-2, Indalpine

65165-99-3 66532-85-2, Propacetamol 66644-81-3, Veralipride
66834-24-0, Cianopramine 67469-69-6, Vanoxerine 67765-04-2
68134-81-6, Gacyclidine 70374-39-9, Lornoxicam 71125-38-7, Meloxicam
71320-77-9, Moclobemide 71620-89-8, Reboxetine 71827-56-0, Clemeprol
72714-74-0, Viqualine 72797-41-2, Tianeptine 73815-11-9, Cimoxatone
74103-06-3, Ketorolac 75991-50-3, Dazepinil 76496-68-9, Levoprotiline
77518-07-1, Amiflamine 79467-22-4, Bipenamol 79617-96-2, Sertraline
79944-58-4, Idazoxan 80018-06-0, Fengabine 80410-36-2 83015-26-3,
Tomoxetine 83366-66-9, Nefazodone 83891-03-6, Norfluoxetine
84057-84-1, Lamotrigine 85650-52-8, 6-Azamianserin 86811-09-8,
Litoxetine 87051-43-2, Ritanserin 89875-86-5, Tiflucarbine
90243-66-6, Montirelin 90293-01-9, Bifemelane 92623-85-3, Milnacipran
93413-69-5, Venlafaxine 93438-65-4, Conantokin G 94011-82-2,
Bazinaprine 96206-92-7, 2-Methyl-6-(phenylethynyl)-pyridine
97205-34-0, Nebracetam 97240-79-4, Topiramate 103628-46-2, Sumatriptan
104054-27-5, Atipamezole 104454-71-9, Ipenoxazone 106650-56-0,
Sibutramine 112922-55-1, Cericlamine 112924-45-5, Dexanabinol
116539-59-4, Duloxetine 117414-74-1, Midafotel 117571-54-7
120667-19-8 121679-13-8, Naratriptan 123653-11-2,
N-[2-(Cyclohexyloxy)-4-nitrophenyl]methanesulfonamide 128196-01-0,
Escitalopram 128298-28-2, Remacemide 132472-31-2,
(3E)-2-Amino-4-(phosphonomethyl)-3-heptenoic acid 134564-82-2,
Befloxatone 135025-56-8, 7-Chlorothiokynurenic acid 137159-92-3,
Aptiganel 137433-06-8, (3S,4AR,6S,8aR)-decahydro-6-(phosphonomethyl)-3-
isoquinolinecarboxylic acid 138047-56-0,
(3R,4S)-rel-3,4-Dihydro-3-[4-hydroxy-4-(phenylmethyl)-1-piperidinyl]-2H-1-
benzopyran-4,7-diol 139051-78-8,
(2R,4S)-rel-5,7-Dichloro-1,2,3,4-tetrahydro-4-
[[(phenylamino)carbonyl]amino]-2-quinolinecarboxylic acid 139264-17-8,
Zolmitriptan 142235-88-9 143322-58-1, Eletriptan 144034-80-0,
Rizatriptan 144912-63-0 149756-73-0 150812-12-7, Retigabine
153322-05-5, Lanicemine 153504-81-5, Licostinel 158747-02-5,
Frovatriptan 160754-76-7, N'-[2-Chloro-5-(methylthio)phenyl]-N-methyl-N-
[3-(methylthio)phenyl]-guanidine 161230-88-2 162011-90-7, Rofecoxib
166974-22-7 169590-41-4, Deracoxib 169590-42-5, Celecoxib
170029-85-3 173186-99-7 180200-68-4,
4-(4-Cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide
181695-72-7, Valdecoxib 186495-49-8, Delucemine 193278-48-7
193359-26-1, 1-[2-(4-Hydroxyphenoxy)ethyl]-4-[(4-methylphenyl)methyl]-4-
piperidinol 197077-52-4, 6,7-Dichloro-1,4-dihydro-5-[3-(methoxymethyl)-5-
(3-pyridinyl)-4H-1,2,4-triazol-4-yl]-2,3-quinoxalinedione 198470-84-7,
Parecoxib 198559-42-1 198710-92-8, Kaitocephalin 200430-63-3,
1,4-Dihydro-6-methyl-5-[(methylamino)methyl]-7-nitro-2,3-quinoxalinedione
202409-33-4, Etoricoxib 202844-10-8,
2-[(2,3-Dihydro-1H-inden-2-yl)amino]-acetamide 212126-32-4,
2-(3,5-Difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one
213980-27-9 219810-59-0, Neramexane 252374-41-7,
1-[4-(1H-Imidazol-4-yl)-3-butynyl]-4-(phenylmethyl)-piperidine
253450-09-8, Besonprodil 266320-83-6 342047-49-8 369640-27-7,
2-Hydroxy-5-[[(pentafluorophenyl)methyl]amino]-benzoic acid 398479-93-1,
M 3-PPC
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(preparation of substituted indole compds. with NOS inhibitory activity
useful as therapeutic agents)

L8 ANSWER 13 OF 14 USPATFULL on STN
ACCESSION NUMBER: 2004:38089 USPATFULL
TITLE: Transdermal delivery of analgesics
INVENTOR(S): Klose, Kathryn Traci-Jane, Chelsea, AUSTRALIA
Colagrande, Felicia Maria, Brunswick, AUSTRALIA
Morgan, Timothy Matthias, Carlton North, AUSTRALIA
Finnin, Barrie Charles, Glen Iris, AUSTRALIA
Reed, Barry Leonard, Strathmore, AUSTRALIA
PATENT ASSIGNEE(S): Monash University (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20040028625	A1	20040212
	US 6916486	B2	20050712
APPLICATION INFO.:	US 2003-428012	A1	20030502 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-910780, filed on 24 Jul 2001, PENDING Division of Ser. No. US 1998-125436, filed on 18 Dec 1998, GRANTED, Pat. No. US 6299900 A 371 of International Ser. No. WO 1997-AU91, filed on 19 Feb 1997, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	AU 1996-8144	19960219

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FOLEY AND LARDNER, SUITE 500, 3000 K STREET NW, WASHINGTON, DC, 20007
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 574
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . opioid analgesics such as buprenorphine, butorphanol, dextromoramide, dezocine, dextropropoxyphene, diamorphine, fentanyl, alfentanil, sufentanil, hydrocodone, hydromorphone, ketobemidone, levomethadyl acetate, mepiridine, methadone, morphine, nalbuphine, opium, oxycodone, papaveretum, pentazocine, pethidine, phenoperidine, piritramide, dextropropoxyphene, remifentanil, tilidine, tramadol, codeine, dihydrocodeine, meptazinol, dezocine, eptazocine and flupirtine.

SUMM . . . the present invention include, but are not limited to chronic pain conditions, post-operative pain, restless leg syndrome, opioid dependence and neuropathic pain.

CLM What is claimed is:
. . . group consisting of opium, butorphanol, dezocine, diamorphine, hydrocodone, ketobemidone, levomethadyl acetate, mepiridine, nalbuphine, piritramide, remifentanil, tilidine, meptazinol, dezocine, eptazocine and flupirtine.

CLM What is claimed is:
. . . to claim 1, wherein the analgesic is selected from the group consisting of tramadol, dextromoramide, dextropropoxyphene, alfentanil, sufentanil, hydromorphone, methadone, morphine, oxycodone, papaveretum, pentazocine, pethidine, phenoperidine, codeine and dihydrocodeine.

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CLM What is claimed is:
. . . group consisting of opium, butorphanol, dezocine, diamorphine, hydrocodone, ketobemidone, levomethadyl acetate, mepiridine, nalbuphine, piritramide, remifentanil, tilidine, meptazinol, dezocine, eptazocine and flupirtine.

CLM What is claimed is:
. . . to claim 11, wherein the analgesic is selected from the group consisting of tramadol, dextromoramide, dextropropoxyphene, alfentanil, sufentanil, hydromorphone, methadone, morphine, oxycodone, papaveretum, pentazocine, pethidine, phenoperidine, codeine and dihydrocodeine.

IT 57-27-2, Morphine, biological studies 57-42-1, Meperidine 64-17-5, Ethanol, biological studies 67-63-0, Isopropanol, biological studies 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 118-60-5, 2-Ethylhexyl salicylate 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 302-41-0, Piritramide 357-56-2, Dextromoramide 359-83-1, Pentazocine 437-38-7, Fentanyl 466-99-9, Hydromorphone 469-62-5, Dextropropoxyphene 469-79-4, Ketobemidone 561-27-3, Diamorphine 562-26-5, Phenoperidine 1477-40-3, Levomethadyl acetate 20594-83-6, Nalbuphine 27203-92-5, Tramadol 42408-82-2, Butorphanol 51931-66-9, Tilidine 52485-79-7, Buprenorphine 53648-55-8, Dezocine 54340-58-8, Meptazinol 56030-54-7, Sufentanil 56995-20-1, Flupirtine 71195-58-9, Alfentanil 72522-13-5, Eptazocine 132875-61-7, Remifentanil
(transdermal delivery of analgesics)

L8 ANSWER 14 OF 14 IMSRESEARCH COPYRIGHT 2010 IMSWORLD on STN

CN flupirtine; flupirtine maleate
RE pINN; USAN
CN W 2964M; D9998
CN KATADOLON; EFFIRMA; METANOR
CN [2-amino-6-[[(4-fluorophenyl)methyl]amino]-3-pyridinyl]carbamic acid (2Z)-2-butenedioate (1:1)
RN 56995-20-1
56995-20-1flupirtine, D9998
33400-45-2 flupirtine monohydrochloride
75507-68-5flupirtine maleate (1:1), W 2964M
56995-21-2replaced by 75507-68-5
105507-11-7 flupirtine mono-D-gluconate
156094-11-0flupirtine mixt with morphine
LI. . . reported that they have entered into a research collaboration; the NNRI will fully fund preclinical studies evaluating the potential of flupirtine, a centrally acting analgesic, in the treatment of retinitis pigmentosa. Flupirtine will be tested in animal models with retinitis pigmentosa, and if positive results are recorded, Adeona and the NNRI will explore progressing flupirtine to clinical trials for this indication.
TX. . . Corporation): US 6610324 2003, priority US 60/128141 1999. Equivalents identified.
TX Commercial Summary: Commercial overview. Meda (formerly Viatris) is developing flupirtine, a centrally acting analgesic. Flupirtine was first launched in Germany in 1985, and has since

been launched in several other markets worldwide for the treatment. . . treatment of retinitis pigmentosa is under way in the USA. Priority product patent applications were filed in August 1964 for flupirtine (specifically) and flupirtine maleate (generically) in West Germany, by Degussa. sanofi-aventis (formerly known as Sanofi-Synthelabo) has rights to the drug in Germany. In November 2005, Pipex (now Adeona) acquired an exclusive license from McLean Hospital (USA) for the use of flupirtine for the treatment of fibromyalgia. In May 2008, Pipex (now Adeona) entered into an option to acquire a license for use of oral flupirtine for the treatment of ophthalmic conditions, diabetes and diabetes-related indications. In August 2008, Meda and Valeant established joint ventures in Australia, Canada and Mexico to develop, market and commercialize products, including flupirtine.Launches. Flupirtine was first launched in Germany in 1985 and then in Brazil in 1991. The drug has also been launched in Portugal and Italy (WSJ, DEC 2000). Flupirtine has been launched in Latvia (IMS, NOV 2003) by PLIVA (now Teva) and in Russia for the treatment of pain. . . progress. An IND has been filed by Pipex (now Adeona) to conduct a double-blind, randomized, placebo-controlled phase II trial of flupirtine for the treatment of fibromyalgia, a rheumatic pain disease. The trial would evaluate safety and efficacy of oral flupirtine versus placebo in patients with fibromyalgia. The trial aims to enroll up to 90 patients and treat them for up. . . issues (Pipex, MAR 2008); the FDA has since approved the IND application to initiate a phase II trial of oral flupirtine for the treatment of fibromyalgia (Pipex, MAY 2008). A phase II trial is under way (Pipex, MAY 2008). Shionogi was evaluating flupirtine in phase II trials in Japan, but studies have been discontinued.A 23-patient clinical trial involving variant Creutzfeldt-Jakob disease infected subjects who received flupirtine or placebo has completed in Germany and preliminary data have been reported. The company plans to file for regulatory approval. . . the National Neurovision Research Institute (NNRI;USA) have entered into a research collaboration; the NNRI will fully fund preclinical studies evaluating flupirtine in animal models of retinitis pigmentosa (National Neurovision Research Institute, Adeona, DEC 2008).Licensing/Partnering. Flupirtine was licensed to Shionogi in 1991.Viatris (now Meda) is investigating this agent as a potential treatment for variant Creutzfeldt-Jakob disease. . . US patent and pending international patents from McLean Hospital (USA), a Harvard University (USA) affiliate, relating to the use of flupirtine for the treatment of fibromyalgia syndrome (Pipex, APR 2008).Pipex (now Adeona) has entered into an option to acquire an exclusive worldwide license to issued and pending patent applications related to additional uses or oral flupirtine for the treatment of a range of ophthalmic conditions, diabetes and diabetes-related indications (Pipex, MAY 2008).Meda and Valeant have established. . . The ventures will manage the regulatory filings and commercialization of the products. The ventures will initially include OX 22 and flupirtine, but may be expanded to include other products. A majority interest in the ventures will be owned by Meda; Valeant. . . a minority interest and participate in a profit share (Meda, Valeant, AUG 2008).

TX Scientific Summary: Preclinical data. In vitro, flupirtine protected against glutamate-induced cytotoxicity in rat hippocampal neurons and in vivo, pretreatment with

the agent reduced infarct size in a mouse model of focal ischemia (Rupalla K, et al; EMBASE: 96008914). Flupirtine was also neuroprotective in retinal ischemia in the rabbit (Osborne NN, et al; EMBASE: 96056067). In anesthetized rats, flupirtine depressed the polysynaptic flexor reflexes without affecting the monosynaptic Hoffmann reflex. The effect on the flexor response was prevented by co-administration of NMDA, but not by co-administration of the non-NMDA agonist alpha-amino-3-hydroxy-5-tertbutyl-4- lisoxazolepropionic acid.Clinical data. Results from a multicenter, double-blind trial of flupirtine for cancer-associated pain, showed that after four weeks. . .

RDAT: . . . product patent application for crystalline maleate filed in West Germany, by Degussa.
AUG 1964 Priority product patent application filed for flupirtine (specifically) and flupirtine maleate (generically) in West Germany, by Degussa.

An alternative to view hit terms when display exceeds KWIC processing limits is to use HIT display format.

=> d his

(FILE 'HOME' ENTERED AT 17:26:33 ON 19 JAN 2010)

FILE 'REGISTRY' ENTERED AT 17:26:48 ON 19 JAN 2010
L1 3 S FLUPIRTINE

FILE 'CA, CAPLUS, IMSPATENTS, IMSRESEARCH, USPATFULL' ENTERED AT 17:28:25 ON 19 JAN 2010
L2 606 S L1
L3 514 S FLUPIRTINE AND MORPHINE
L4 216 S L2 AND L3
L5 25214 S NEUROPATHIC
L6 23473 S NEURO? PAIN
L7 23 S L6 AND L4
L8 14 DUP REM L7 (9 DUPLICATES REMOVED)
L9 0 S L8 AND PY<2004

=> s flupirtine or l1
L10 1005 FLUPIRTINE OR L1

=> s fentanyl or oxycodone or codeine or dihydrocodeine or dihydrocodeinone or morphine or desomorphine or apomorphine or diamorphine or pethidine or methadone or dextropropoxyphene or propoxyphen or pentazocine or dextromoramide or oxymorphone or hydromorphone or dihydromorphine
THE ESTIMATED SEARCH COST FOR FILE 'CA' IS 39.24 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
THE ESTIMATED SEARCH COST FOR FILE 'CAPLUS' IS 41.58 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
2 FILES SEARCHED...
L11 168582 FENTANYL OR OXYCODONE OR CODEINE OR DIHYDROCODEINE OR DIHYDROCODEINONE OR MORPHINE OR DESOMORPHINE OR APOMORPHINE OR DIAMORPHINE OR PETHIDINE OR METHADONE OR DEXTROPROPOXYPHENE OR PROPOXYPHEN

```
               OR PENTAZOCINE OR DEXTROMORAMIDE OR OXYMORPHONE OR HYDROMORPHONE
                OR DIHYDROMORPHINE

=> s noscapine or papaverine or papaveretum or alfentanil or buprenorphine
L12      34271 NOSCAPINE OR PAPAVERINE OR PAPAVERETUM OR ALFENTANIL OR BUPRENOR
               PHINE

=> s l11 or l12
L13     188740 L11 OR L12

=> s l13 and l10
L14        570 L13 AND L10

=> s l14 and l6
L15         96 L14 AND L6

=>  parenteral or or
PARENTERAL IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s parenteral or oral or vaginal or intravesical or subcutaneous or intramuscular
or intravenous or intrasternal or intrathecal or epidural or intradermal
THE ESTIMATED SEARCH COST FOR FILE 'CA' IS 23.98 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
THE ESTIMATED SEARCH COST FOR FILE 'CAPLUS' IS 25.41 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
L16    1069196 PARENTERAL OR ORAL OR VAGINAL OR INTRAVESICAL OR SUBCUTANEOUS
               OR INTRAMUSCULAR OR INTRAVENOUS OR INTRASTERNAL OR INTRATHECAL
               OR EPIDURAL OR INTRADERMAL

=> s l15 and l16
L17         81 L15 AND L16

=> s l17 and py<2004
L18          4 L17 AND PY<2004

=> d l18 1-4 ibib, kwic

L18  ANSWER 1 OF 4  USPATFULL on STN
ACCESSION NUMBER:       2003:119740  USPATFULL
TITLE:                  Sterile, breathable patch for treating wound pain
INVENTOR(S):            Mason, Paul Arthur, Flemington, NJ, UNITED STATES

                             NUMBER       KIND    DATE
                        ---------------- ------ --------
PATENT INFORMATION:     US 20030082225     A1   20030501            <--
APPLICATION INFO.:      US 2001-45730      A1   20011019  (10)
DOCUMENT TYPE:          Utility
FILE SEGMENT:           APPLICATION
LEGAL REPRESENTATIVE:   PENNIE AND EDMONDS, 1155 AVENUE OF THE AMERICAS, NEW
                        YORK, NY, 100362711
NUMBER OF CLAIMS:       53
EXEMPLARY CLAIM:        1
LINE COUNT:             1480
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An intradermal patch having a permeable backing coated with a polyvinylpyrrolidone-based hydrogel and containing one or more local anesthetics. The patch is. . .

SUMM . . . for example, TRANSDERMAL AND TOPICAL DRUG DELIVERY SYSTEMS 87-93 (Tapash K. Ghosh et al. eds., 1997) and opioids, such as morphine. See e.g., U.S. Pat. No. 5,948,389 (issued Sep. 7, 1999); Christoph Stein & Alexander Yassouridis 71 Pain 119 (1997).

SUMM [0005] N-methyl-D-aspartate ("NMDA") receptor antagonists, such as ketamine also have local-anesthetic properties and topical administration is as an effective neuropathic pain treatment. See, for example, U.S. Pat. No. 5,817,699 (issued Oct. 6, 1998). In another example, topical administration of antidepressant medications, such as amitriptyline, has been reported effective for neuropathic pain treatment. See, for example, U.S. Pat. No. 6,211,171 (issued Apr. 3, 2001); J. Sawynok et al., 82 PAIN 149 (1999).. . . and an NMDA-receptor antagonist is reported to have excellent local-anesthetic properties when topically applied and is useful for treatment of neuropathic pain, U.S. Pat. No. 6,197,830 (issued Mar. 6, 2001).

SUMM [0016] As used herein, a "patch of the invention" means an intradermal delivery patch comprising a breathable backing coated with a polyvinylpyrrolidone-based hydrogel, the hydrogel comprising one or more local anesthetics or. . .

SUMM [0022] As used herein, the term "wound" refers broadly to injuries to the skin and subcutaneous tissue. Wounds may be classified into one of four grades depending on the depth of the wound: Grade I: wounds limited to the epithelium; Grade II: wounds extending into the dermis; Grade II: wounds extending into the subcutaneous tissue; and Grade IV (or full-thickness wounds): wounds wherein bones are exposed. The term "wound" further includes infected wounds, chronic. . .

SUMM . . . herein, a "therapeutically effective amount" of a local anesthetic means the amount of the local anesthetic required in a topical, intradermal patch of the invention to induce a local-anesthetic effect sufficient to treat or ameliorate pain in a mammal.

SUMM [0026] As used herein, the term "intradermal administration" means administration of a pharmaceutical to the skin of a mammal, preferably a human, to deliver the pharmaceutical to the local tissue under and around the site of administration. Preferably, intradermal administration is effected without significant absorption of the pharmaceutical into the mammal's blood stream. The purpose of intradermal administration is to elicit a local affect in contrast to transdermal administration where the objective is to transfer the pharmaceutical. . .

SUMM [0027] As used herein, the phrases "topical administration" and "topical delivery" of a pharmaceutical (e.g., a local anesthetic) means intradermal administration of the pharmaceutical by topical application of the pharmaceutical or a patch or composition comprising the pharmaceutical. For example,. . .

SUMM . . . phrase "intradermally acceptable" means any pharmaceutical, excipient or other component of a topical formulation that is safe or approved for intradermal or topical administration in mammals.

SUMM [0042] Opioids and pharmaceutically acceptable salts thereof, such as

morphine are known to have local-anesthetic properties when topically administered in mammals. See, for example, U.S. Pat. No. 5,948,389 (issued Sep.. . .

SUMM [0044] Examples of suitable opioids include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, benzitramide, nor-binaltorphimine, bremazocine, buprenorphine, butorphanol, clonitazene, codeine, CTOP, DAMGO, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydrocodeine enol acetate, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprenorphine, DPDPE, eptazocine, ethoheptazine, ethylketocyclazocine, ethylmethylthiambutene, etonitazene, etorphine, fentanyl, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, lofentanil, loperamide, meperidine, meptazinol, metazocaine, methadone, metopon, morphine , myrophine, nalbuphine, naltrindole, benzoylhydrazone, naltrexone, narceine, nicomorphine, norlevorphanol, normethadone, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, papaverine, pentazocine, phenadoxone, phenazocine, phenoperidine, piminodine, pirtramide, proheptazine, promedol, propiram, propoxyphene, remifentanil, spiradoline, sufentanil, tilidine, U50,488, and U69,593, amiphenazole, cyclazocine, levallorphan, nalmefene,. . .

SUMM . . . Tyr-D-Ala-Phe-Glu-Val-Val-Gly-NH.sub.2 ([D-Ala.sup.2Glu.sup.4]Deltorphin (Deltorphin II)), Tyr-Pro-Phe-Pro-NH.sup.2 (Morphiceptin), Tyr-Pro-MePhe-D-Pro-NH.sup.2 (PL-017), [D-Ala.sup.2,Leu.sup.5,Cys.sup.6]enkephalin (DALCE) or pharmaceutically-acceptable salts thereof, or mixtures thereof. Preferred opioids include morphine, loperamide, and loperamide derivatives such as those disclosed in U.S. Pat. Nos. 5,763,445; 5,981,513; 5,869,521; 5,744,458; 5,760,023; 5,798,093; 5,849,762; 5,811,078;. . . thereof, or mixtures thereof, all of which patents are hereby expressly incorporated herein by reference. The most preferred opioid is morphine or a pharmaceutically-acceptable salt thereof.

SUMM [0049] Notably, the intradermal patches of the invention involve topical administration, thus "antidepressants" unsuitable for systemic administration in mammals, because of toxicity or otherwise,. . .

SUMM [0081] Other NMDA-receptor antagonists include, but are not limited to, amantadine, eliprodil, iamotrigine, riluzole, aptiganel, flupirtine, celfotel, levemopamil, 1-(4-hydroxyphenyl)-2-(4-phenylsulfanyl-piperidin-1-yl)-propan-1-one; 2-[4-(4-fluoro-benzoyl)-piperidin-1-yl]-1-naphthalen-2-yl-ethanone (E 2001); 3-(1,1-dimethyl-heptyl)-9-hydroxymethyl-6,6-dimethyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol (HU-211); 1-{4-[1-(4-chloro-phenyl)-1-methyl-ethyl]-2-methoxy-phenyl}-1H-[1,2,4]triazole-3-carboxylic acid amide (CGP 31358); acetic acid 10-hydroxy-7,9,7',9'-tetramethoxy-3,3'-dimethyl-3,4,3',4'-tetrahydro-1H,1H-[5,5']bi[benzo[g]isochromenyl]-4-yl ester (ES 242-1); 14-hydroxy-11-isopropyl-10-methyl-5-octyl-10,13-diaza-tricyclo[6.6.1.04,15]pentadeca-1,4,6,8(15)-tetraen-12-one;. . .

SUMM . . . in patches of the invention is a combination of an opioid and a sodium-channel blocker, such as a mixture of morphine or a pharmaceutically acceptable salt thereof and lidocaine or a

pharmaceutically acceptable salt thereof.

SUMM . . . of the invention can include medicinal agents or their pharmaceutically acceptable salts. Medicinal agents are compounds that upon transdermal or intradermal adsorption have a pharmaceutical effect. When used, preferably, the medicinal agent is added to the pre-hydrogel mixture during patch manufacture.. . .

SUMM . . . stimulation of peripheral nociceptors. The patches and methods of the invention are effective to induce local anesthesia and to treat neuropathic pain. As used herein the term " neuropathic pain" refers to neuropathic-pain syndromes, that is, pain due to lesions or dysfunction in the nervous system. The patches and methods of the invention. . .

SUMM [0145] Selection of the appropriate dosage of local anesthetic for the application site is an important consideration. The rate of intradermal anesthetic delivery from a patch of the invention is a function of the application site, for example, whether the patch. . .

CLM What is claimed is:
11. The patch of claim 5, wherein the opioid is morphine or a pharmaceutically acceptable salt thereof.

CLM What is claimed is:
21. The package of claim 15, wherein the opioid is morphine or a pharmaceutically acceptable salt thereof.

CLM What is claimed is:
32. The method of claim 26, wherein the opioid is morphine or a pharmaceutically acceptable salt thereof.

CLM What is claimed is:
43. The method of claim 37, wherein the opioid is morphine or a pharmaceutically acceptable salt thereof.

CLM What is claimed is:
53. The polyvinylpyrrolidone-based hydrogel of claim 47, wherein the opioid is morphine or a pharmaceutically acceptable salt thereof.

IT 50-48-6, Amitriptyline 57-27-2, Morphine, biological studies 73-78-9, Lidocaine hydrochloride 137-58-6, Lidocaine 6740-88-1, Ketamine 8066-38-4, Phenonip 9003-39-8, Polyvinylpyrrolidone
(sterile and breathable patch for treating wound pain)

L18 ANSWER 2 OF 4 USPATFULL on STN
ACCESSION NUMBER: 2003:119729 USPATFULL
TITLE: Topical compositions and methods for treating pain
INVENTOR(S): Williams, Robert O., Austin, TX, UNITED STATES
Zhang, Feng, Austin, TX, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20030082214	A1	20030501	<--
	US 6638981	B2	20031028	
APPLICATION INFO.:	US 2001-931293	A1	20010817 (9)	

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION

10574438

LEGAL REPRESENTATIVE: PENNIE AND EDMONDS, 1155 AVENUE OF THE AMERICAS, NEW YORK, NY, 100362711
NUMBER OF CLAIMS: 57
EXEMPLARY CLAIM: 1
LINE COUNT: 2008
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . surfactant. The compositions induce a local-anesthetic effect when topically administered to intact skin thereby treating or preventing pain, for example, neuropathic pain.

SUMM . . . or skin pinch), which then transmit impulses over intact neural pathways to the spinal neurons and then to the brain. Neuropathic pain is caused by damage to neural structures, such as damage to peripheral nerve endings or nociceptors, which become extremely sensitive. . .

SUMM . . . for example, TRANSDERMAL AND TOPICAL DRUG DELIVERY SYSTEMS 87-93 (Tapash K. Ghosh et al. eds., 1997) and opioids, such as morphine. See e.g., U.S. Pat. No. 5,948,389 (issued Sept. 7, 1999); Christoph Stein & Alexander Yassouridis 71 Pain 119 (1997).

SUMM [0005] N-methyl-D-aspartate ("NMDA") receptor antagonists, such as ketamine have local-aesthetic properties and topical administration is as an effective neuropathic pain treatment. See, for example, U.S. Pat. No. 5,817,699 (issued Oct. 6, 1998). In another example, topical administration of antidepressant medications, such as amitriptyline, has been reported effective for neuropathic pain treatment. See, for example, U.S. Pat. No. 6,211,171 (issued Apr. 3, 2001); J. Sawynok et al., 82 PAIN 149 (1999).. . . and an NMDA-receptor antagonist is reported to have excellent local-anesthetic properties when topically applied and is useful for treatment of neuropathic pain, U.S. Pat. No. 6,197,830 (issued Mar. 6, 2001).

SUMM . . . skin is routinely used to treat minor indications, it has not found significant use for treating more severe nociceptive and neuropathic pain because it is difficult to get significant concentrations through the skin barrier. Because of the skin's drug-permeation resistance, as little. . .

SUMM . . . invention can be topically administered to intact skin to provide a local-anesthetic effect thereby treating or preventing pain, for example, neuropathic pain. In one embodiment, the invention provides stable, skin penetrating compositions for topical administration comprising a combination of an antidepressant and. . .

SUMM [0046] As used herein, the term "intradermal administration" means administration of a pharmaceutical to the skin of a mammal, preferably a human, to deliver the pharmaceutical to the local tissue under and around the site of administration. Preferably, intradermal administration is effected without absorption of the pharmaceutical into the mammal's blood stream. The purpose of intradermal administration is to elicit a local affect in contrast to transdermal administration where the objective is to transfer the pharmaceutical. . .

SUMM [0047] As used herein, the term "topical administration" or "topical delivery" means intradermal administration of a pharmaceutical by administration of the pharmaceutical or a composition comprising the pharmaceutical to intact skin. For example, by rubbing a composition of the invention onto an area of intact skin or by placing an intradermal patch comprising a composition of the invention onto

an area of intact skin.

SUMM . . . the phrase "intradermally-acceptable" means any pharmaceutical, excipient or other component of a topical formulation that is safe or approved for intradermal or topical administration in mammals.

SUMM . . . NMDA-receptor antagonist through intact skin at a high flux rate to induce local anesthesia and thereby treat, ameliorate, or prevent neuropathic pain. Furthermore, the compositions of the invention are stable both physically (resists coalescing of droplets and Ostwald ripening) and chemically stable. . .

SUMM . . . stimulation of peripheral nociceptors. The compositions and methods of the invention are effective to induce local anesthesia and to treat neuropathic pain. As used herein the term " neuropathic pain" refers to neuropathic-pain syndromes, that is, pain due to lesions or dysfunction in the nervous system. The compositions and methods of the invention. . .

SUMM [0113] Other NMDA-receptor antagonists include, but are not limited to, amantadine, eliprodil, iamotrigine, riluzole, aptiganel, flupirtine, celfotel, levemopamil, 1-(4-hydroxy-phenyl)-2-(4-phenylsulfanyl-piperidin-1-yl)-propan-1-one; 2-[4-(4-fluoro-benzoyl)-piperidin-1-yl]-1-naphthalen-2-yl-ethanone (E 2001); 3-(1,1-dimethyl-heptyl)-9-hydroxymethyl-6,6-dimethyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol (HU-211); 1-{4-[1-(4-chloro-phenyl)-1-methyl-ethyl]-2-methoxy-phenyl}-1H-[1,2,4]triazole-3-carboxylic acid amide (CGP 31358); acetic acid 10-hydroxy-7,9,7',9'-tetramethoxy-3,3'-dimethyl-3,4,3',4'-tetrahydro-1H,1'H-[5,5']bi[benzo[g]isochromenyl]-4-yl ester (ES 242-1);. . .

SUMM . . . material or mixture of materials that can form a stable emulsion comprising an antidepressant and an NMDA-receptor antagonist, suitable for intradermal administration. Preferably, the lipophilic component comprises about 15% to about 40% by weight of the total composition weight, more preferably,. . .

SUMM . . . material that facilitates absorption of the antidepressant and the NMDA-receptor antagonist into the skin, referred to herein as a "lipophilic intradermal-penetration enhancer". The preferred amount of lipophilic-intradermal-penetration enhancer is about 1% to about 15% by weight of the total composition weight. Suitable lipophilic intradermal penetration enhancers include isopropyl myristate, glycerol monolaurate, glycerol monooleate, glycerol monolinoleate, isopropyl isostearate, isopropyl linoleate, isopropyl myristate/fatty acid monoglyceride combination,. . .

SUMM [0147] Opioids, such as morphine are known to have local-anesthetic properties when topically administered in mammals. See, for example, U.S. Pat. No. 5,948,389 (issued Sep.. . .

SUMM [0149] Examples of suitable opioids include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, benzitramide, nor-binaltorphimine, bremazocine, buprenorphine, butorphanol, clonitazene, codeine, CTOP, DAMGO, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydrocodeine enol acetate, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprenorphine, DPDPE, eptazocine, ethoheptazine, ethylketocyclazocine, ethylmethylthiambutene, etonitazene, etorphine, fentanyl, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, lofentanil, loperamide, meperidine,

meptazinol, metazocaine, methadone, metopon, morphine , myrophine, nalbuphine, naltrindole, benzoylhydrazone, naltrexone, narceine, nicomorphine, norlevorphanol, normethadone, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, papaverine, pentazocine, phenadoxone, henazocine, phenoperidine, piminodine, pirtramide, proheptazine, promedol, propiram, propoxyphene, remifentanil, spiradoline, sufentanil, tilidine, U50,488, and U69,593, amiphenazole, cyclazocine, levallorphan, nalmefene,. . .

SUMM . . . Tyr-D-Ala-Phe-Glu-Val-Val-Gly-NH.sub.2 ([D-Ala.sup.2Glu.sup.4]Deltorphin (Deltorphin II)), Tyr-Pro-Phe-Pro-NH.sup.2 (Morphiceptin), Tyr-Pro-MePhe-D-Pro-NH.sup.2 (PL-017), [D-Ala.sup.2,Leu.sup.5,Cys.sup.6]enkephalin (DALCE) or pharmaceutically-acceptable salts thereof, or mixtures thereof. Preferred opioids include morphine, loperamide, and loperamide derivatives such as those disclosed in U.S. Pat. Nos. 5,763,445; 5,981,513; 5,869,521; 5,744,458; 5,760,023; 5,798,093; 5,849,762; 5,811,078;. . . thereof, or mixtures thereof, all of which patents are hereby expressly incorporated herein by reference. The most preferred opioid is morphine or a pharmaceutically-acceptable salt thereof.

SUMM [0170] 2. Administration via an Intradermal Patch

SUMM [0185] Selection of the appropriate dosage for the application site is an important consideration. The rate of intradermal anesthetic administration from the topical formulation or patch is a function of skin permeability, and skin permeability has been shown. . .

CLM What is claimed is:
19. The emulsion of claim 1, further comprising a lipophilic intradermal penetration enhancer.

CLM What is claimed is:
20. The emulsion of claim 19, wherein the lipophilic intradermal penetration enhancer is isopropyl myristate, glycerol monolaurate, glycerol monooleate, glycerol monolinoleate, isopropyl isostearate, isopropyl linoleate, isopropyl myristate/fatty acid monoglyceride combination,. . .

CLM What is claimed is:
39. The method of claim 24, wherein the emulsion further comprises a lipophilic intradermal penetration enhancer.

CLM What is claimed is:
40. The method of claim 39, wherein the lipophilic intradermal penetration enhancer is isopropyl myristate, glycerol monolaurate, glycerol monooleate, glycerol monolinoleate, isopropyl isostearate, isopropyl linoleate, isopropyl myristate/fatty acid monoglyceride combination,. . .

CLM What is claimed is:
56. The method of claim 41, wherein the emulsion further comprises a lipophilic intradermal penetration enhancer.

CLM What is claimed is:
57. The method of claim 56, wherein the lipophilic intradermal penetration enhancer is isopropyl myristate, glycerol monolaurate, glycerol monooleate, glycerol monolinoleate, isopropyl isostearate, isopropyl linoleate, isopropyl myristate/fatty acid monoglyceride combination,. . .

L18 ANSWER 3 OF 4 USPATFULL on STN
ACCESSION NUMBER: 2000:121543 USPATFULL
TITLE: Use of retigabine for the treatment of neuropathic pain
INVENTOR(S): Rundfeldt, Chris, Coswig, Germany, Federal Republic of
Bartsch, Reni, Ottendorf-Okrilla, Germany, Federal Republic of
Rostock, Angelika, Radebeul, Germany, Federal Republic of
Tober, Christine, Weinbohla, Germany, Federal Republic of
Dost, Rita, Dresden, Germany, Federal Republic of
PATENT ASSIGNEE(S): ASTA Medica Aktiengesellschaft, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6117900		20000912	<--
APPLICATION INFO.:	US 1999-406135		19990927 (9)	

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Spivack, Phyllis G.
LEGAL REPRESENTATIVE: Pillsbury Madison & Sutro LLP
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
LINE COUNT: 440
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Use of retigabine for the treatment of neuropathic pain

AB . . . to the use of 2-amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylaminobenzene of formula I ##STR1## or its pharmaceutically utilizable salts, for the prophylaxis and treatment of neuropathic pain.

SUMM . . . of 2-amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylaminobenzene of the formula I ##STR2## (INN: retigabine) or its pharmaceutically utilizable salts for the prophylaxis and treatment of neuropathic pain.

SUMM Neuropathic pain such as allodynia and hyperalgesia describes a particular type of pain sensation which differs from the customary perception of painful. . .

SUMM . . . has been amputated. In the scientific literature, this type of pain sensation is often subsumed under the term centrally mediated neuropathic pain. It is characteristic here that the actual pain sensation is not be attributed to a customary pain-inducing stimulus, but is. . . nervous system, as the level or reaction of the pain-sensing and pain-transmitting system is altered. Unlike other forms of pain, neuropathic pain is usually chronic and customarily cannot be treated or can only be treated with difficulty with conventional analgesics such as. . .

SUMM . . . with high doses of cytostatics for cancer treatment, patients often also report pain sensations (Brant 1998; Brant J M, Cancer-related neuropathic pain. Nurse Pract. Forum. September 1998; 9 (3): 154-62). Tanner et al. (Tanner K D; Reichling D B; Levine J D,. . .

SUMM 5. A tumour disorder itself can also elicit neuropathic pain (e.g. as a result of chronic nerve compression by the tumour) which belongs to the hyperalgesia type (Brant 1998; Brant J M, Cancer-related neuropathic pain. Nurse Pract. Forum, September 1998; 9 (3): 154-62).

SUMM . . . a widespread form of hyperalgesia which often occurs without visible damage to the nerves (Burchiel, 1993; Burchiel K J, Trigeminal neuropathic pain. Acta Neurochir. Suppl. Wien. 1993; 58; 145-9).

SUMM . . . spite of this a large proportion of the patients additionally complain about pain sensations. These persistent sensations are described as neuropathic pain and can be delimited diagnostically from other (inflammatory) forms of pain (Sorensen and Bengtsson, 1997; Sorensen J; Bengtsson M, Intravenous phentolamine test--an aid in the evaluation of patients with persistent pain after low-back surgery? Acta Anaesthesiol. Scand. May 1997; 41. . .

SUMM . . . of intact spinal cord and are not to be related to a painful stimulus. This pain is described as central neuropathic pain (Eide 1998; Eide P K, Pathophysiological mechanisms of central neuropathic pain after spinal cord injury. Spinal cord. September 1998; 36 (9): 601-12).

SUMM 12. Pain occurring after amputations has characteristics of neuropathic pain (Hill 1999; Hill A, Phantom limb pain: a review of the literature on attributes and potential mechanisms. J. Pain Symptom. . .

SUMM . . . nature of the modified pain reaction can be very different. It is common to all these pain reactions, however, that morphines are either inactive or only act when using doses which cause undesired side effects. Triggering factors for the pain reaction. . .

SUMM . . . J Pharmacol Exp Ther. March 1999; 288 (3): 1026-30). By means of gabapentine, a medicament having a marked action in neuropathic pain, the spontaneous activity of these nerve cell foci (ectopic foci) can be suppressed in a dose-dependent manner. In the same. . . in mice. Eur. J. Pharmacol. May 22, 1998; 349 (2-3): 211-20). Investigations in which it was possible to show that intrathecal administration of NMDA antagonists were able to reduce the pain also point to the involvement of the NMDA receptor. In. . .

SUMM . . . pain sensation and the nerve cell-protecting treatment of the causes of the disorder (Morz 1999, Morz R; Schmerzbehandlung bei diabetischen Neuropathien (Pain treatment in diabetic neuropathies), Fortschritte der Medizin 1999, 13: 29-30). In patients with diabetes-related neuropathic pain, the optimization of the metabolic levels to avoid further progression and the prevention of subsequent damage such as foot lesions. . .

SUMM The actual symptomatic pain therapy, however, must resort to other medicaments. Neither centrally active analgesics such as morphine derivatives nor customary peripherally active analgesics such as paracetamol or acetylsalicylic acid are effective. However, antidepressants such as amitriptyline, imipramine. . .

SUMM . . . literature, for example, the use of topiramate (U.S. Pat. No. 5,760,007) and moxonidine (EP 901 790) for the treatment of neuropathic pain is demonstrated.

SUMM . . . All medicaments mentioned, however, only lead to an alleviation of the pain symptoms in some of the patients. In herpes-induced

neuropathic pain, it is possible prophylatically by the use of virostatics to protect the nerve cell causally from the harmful action of the virus at an early point in time of the disorder and thereby to reduce the expression of the neuropathic pain; these medicaments, however, are not effective symptomatically after the acute infection subsides. Affected patients can experience alleviation of the symptoms. . .

SUMM In compression-related neuropathic pain, it is possible to eliminate the primary cause of the disorder, for example, in the carpal tunnel syndrome or on. . . or gabapentine are used. In the case of amputation pain, the actual cause, the amputation, cannot be treated, so that neuropathic pain has to be treated only symptomatically with the abovementioned groups of medicaments. However, it has been attempted recently in the case of systematic amputations to counteract the development of neuropathic pain by conduction blockade of the nerves to be severed for several days before carrying out the amputation. Although the first. . .

DETD In summary, it can be established that for the symptomatic treatment of neuropathic pain conventional analgesics have a low efficacy. Medicaments such as antidepressants, carbamazepine or valproate are used, which per se have no. . .

DETD The aim of this invention is to make available a substance with which the pain symptoms of neuropathic pain can be treated.

DETD Surprisingly, it has now been found that retigabine of the formula I ##STR3## has significant activities against neuropathic pain. Thus entirely new possibilities for the prophylaxis and treatment of neuropathic pain open up.

DETD Retigabine is a derivative of the non-opioid analgesic flupirtine, for which an anticonvulsive action was also demonstrated in addition to its analgesic action. By means of structural optimization with. . . modelling to separate the anticonvulsant from the analgesic action in this substance class. Retigabine has a stronger anticonvulsant action than flupirtine, but an analgesic action in models of acute pain is no longer detectable (Rostock et al., 1996; Rostock A; Tober. . .

DETD Unexpectedly, we were able to establish that retigabine has marked dose-dependent action against neuropathic pain. As expected, however, the analgesic action, as is seen in this model in the early phase, was only low and. . .

DETD In this model, a biphasic nocifensive behaviour reaction is induced by the subcutaneous injection of low-percentage formalin (Field et al. 1997; Field M J; Oles R J; Lewis A S; McCleary S; Hughes. . .

DETD . . . 15 min before the start of the experiment. 0.05 ml of 2.5% formaldehyde in isotonic saline solution given by plantar subcutaneous injection in the hind paw brought about a severe immediate reaction with biting and licking of a few minutes duration. . .

DETD Retigabine inhibited the late phase of the pain reactions, to be described as hyperalgesia or neuropathic pain, in a dose-dependent manner after 5, 10 and 20 mg/kg orally. The action of 10 mg/kg of retigabine corresponded approximately to the effect of 60 mg/kg of oral gabapentine (see Table 1).

DETD TABLE 1

Effect of retigabine on the hyperalgesia of rats after oral administration
Sum of the behaviour score over 5 min averaged staring from Treatment Dose formalin administration (average value ± standard. . .

DETD In the case of oral or parenteral administration, the daily dose of the compound of the formula I should be 50-500 mg. Preferably, individual doses of 30-60 mg are administered in the case of oral administration and 5-20 mg in the case of parenteral administration (the amounts are in each case based on the free base). If necessary, it is possible to depart from. . .

CLM What is claimed is:
2. The method of claim 1 wherein said pain is selected from the group consisting of neuropathic pain, allodynia, hyperalgesic pain and phantom pain.

CLM What is claimed is:
3. The method of claim 2 wherein said pain is neuropathic pain.

CLM What is claimed is:
4. The method of claim 3 wherein said pain is neuropathic pain in migraine.

CLM What is claimed is:
5. The method of claim 3 wherein said pain is neuropathic pain in diabetic neuropathy.

ST retigabine pain treatment; neuropathic pain treatment
retigabine
IT Nerve, disease
(neuropathy, neuropathic pain; retigabine for treatment of pain)

L18 ANSWER 4 OF 4 USPATFULL on STN

ACCESSION NUMBER:	2000:15651 USPATFULL		
TITLE:	Use of substituted 2,4-imidazolidinedione compounds as analgesics		
INVENTOR(S):	Zimmer, Oswald, Wuerselen, Germany, Federal Republic of Selve, Norma, Aachen, Germany, Federal Republic of		
PATENT ASSIGNEE(S):	Gruenenthal GmbH, Aachen, Germany, Federal Republic of (non-U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6022875		20000208 <--
APPLICATION INFO.:	US 1998-126753		19980731 (9)
	NUMBER		DATE
PRIORITY INFORMATION:	DE 1997-19732928		19970731
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Jarvis, William R. A.		
LEGAL REPRESENTATIVE:	Evenson, McKeown, Edwards & Lenahan, P.L.L.C.		
NUMBER OF CLAIMS:	6		

10574438

EXEMPLARY CLAIM: 1
LINE COUNT: 274
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . system but also by disrupted perception and processing and disruption of the descending, controlling, endogenic pain-relieving system. In chronic or neuropathic pain, various phenomena occur including sensitisation of the nocisensors by endogenic or exogenic substances. In the event of persistent stimulation or. . .

SUMM . . . substances are selected from at least one of the groups opioids, tramadol material and non-opioid analgesics. Examples of opioids include morphine, hydromorphone, codeine, oxycodone, dihydrocodeine, dextropropoxyphene, buprenorphine, levomethadone, fentanyl, sufentanil, together with the pharmaceutical salts of the above-stated active substances. Tramadol material comprises tramadol [(1RS;2RS)-2-[(dimethylamino)methyl]-1-(3-methoxy-phenyl)cyclohexanol)], tramadol N-oxide, O-demethyl-tramadol, the. . . example piroxicam and tenoxicam, non-acidic, non-opioid anilines and pyrazolinones, for example paracetamol and metamizol, together with non-opioid pyridylcarbamates, for example flupirtine and benzoxazocines, for example nefopam.

SUMM . . . the production of pharmaceutical preparations for the treatment of chronic pain conditions. Chronic pain conditions, i.e. chronic inflammatory and chronic neuropathic pain conditions, occur, for example, in rheumatism, secondary inflammatory osteoarthrosis, back pain, tension headaches, trauma, herpes zoster and trigeminal neuralgia.

SUMM . . . analgesic to be produced is to be administered orally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally, buccally or locally. Preparations suitable for oral administration are those in the form of matrix tablets, coated tablets, multi-layer tablets, chewable tablets, sugar-coated tablets, capsules, pellets, drops, elixirs or syrups, those suitable for parenteral, topical and inhalatory application are in the form of solutions, suspensions, readily reconstitutable dry preparations and sprays. Compounds according to. . . are examples of suitable percutaneous dosage forms. Delayed release of the compounds according to the invention may be achieved with oral or percutaneous preparations.

DETD . . . 128.7 (97.5-152.6)

Vehicle (aqueous carboxymethyl-cellulose suspension)	2.3-19.8	
Compound 3	46.4	14.5 ± 5.96
Tramadol	2.15	13.5 ± 3.45
Compound 3 and Tramadol	46.4 and 2.15	47.9 ± 8.77
Morphine	1.46	12.0 ± 4.56
Compound 3 and Morphine	46.4 and 1.46	23.3 ± 4.84
Metamizol	21.5	5.1 ± 3.86

Compound 3 and Metamizol	46.4 and 21.5	41.5 ± 11.52
Acetylsalicylic acid (ASA)	464	1.1 ± 3.68
Compound 3 and		
. . .		